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ORIGINAL ARTICLES

THE DETERMINATION OF LACTIC ACID IN BLOOD*

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DURING the past few years we have had occasion frequently to determine the amount of lactic acid in blood, and occasionally in urine. We have used the method of Von Fürth and Charnass† but have found that there are various parts of the process in which considerable errors are liable to be made unless great care is exercised. In the present paper we are recording some of our experiences with the method as used with the modifications which we have introduced to avoid error. The method is inapplicable for urine without very considerable modifications and even with these the results, in our hands, were not very satisfactory. The present paper relates to the method for blood.

Since the method is apparently not well known among British and American workers we will first of all describe it in detail as used in this laboratory. A flask containing 100 c.c. of 2 per cent HCl is weighed, and from 25 to 50 c.c. blood is delivered into it, after which it is immediately reweighed and sufficient of a 5 per cent solution of $HgCl_2$ added to precipitate all the proteins. We have found that 80 c.c. of this solution is necessary for 50 grams of blood. When less blood is taken, proportionately less $HgCl_2$ solution should be used, so as not to increase the bulk of the HgS precipitate formed in the next stage. The mixture is made up to 250 c.c. with water, and is well shaken. After precipitation, or in about 30 mins. it is filtered through thin folded filter paper until as much filtrate comes through as possible. The excess of mercury is then precipitated by hydrogen sulphide, the precipitate removed by filtration and

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†Von Fürth and Charnass: Biochem. Ztschr., 1910, xxvi 199, also Analyse des Harns (Wiesbaden), 1910, i, 233.

the filtrate accurately measured. An aliquot part, 175 c.c. (7/10ths) of the original solution can usually be secured, is taken for further analysis. This measured portion is then almost neutralized towards litmus with sodium hydroxide 4 per cent and placed in a large flat porcelain photographic developing tray with a lip at one corner. The bulk is reduced by evaporation in a warmed air stream. We have found that a large sized majestic heater working in line with a large sized office fan, quite rapidly reduces the solution. It is very important that the temperature during evaporation should never rise above 40° C. since above this temperature, even in faintly acid solutions, there is a decided loss of lactic acid. Under the above conditions, because of the rapid evaporation, the temperature rarely rises above 20° C.

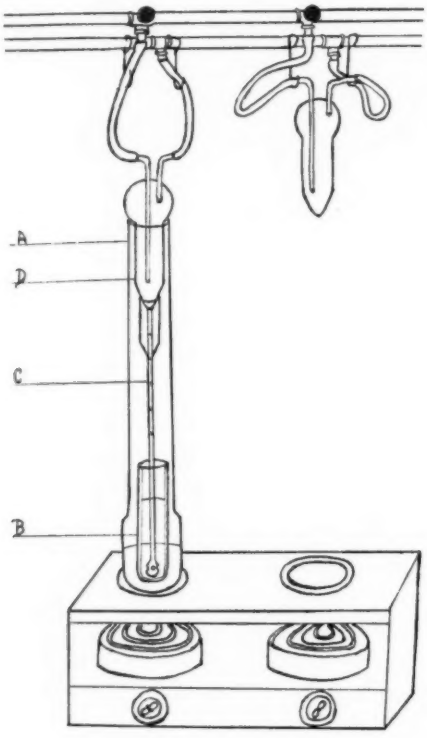

Fig. 1.

Evaporation is allowed to proceed until the volume is reduced to 50 c.c. (2 to 3 hours) and this is then transferred to the extraction tube of the Dunbar apparatus (vide infra). The photographic dish is washed into the tube by means of about 25 c.c. of saturated solution of Amonium sulphate in three portions, and the fluid in the tube is saturated with ammonium sulphate (about 50 grams), 3 c.c. phosphoric acid added, and extraction is allowed to proceed for 48 hrs.

The Dunbar apparatus (see Fig. 1) consists of an outer glass cylinder bulged below (A), an extraction tube (B) having a loop of thin aluminum wire attached at its upper end, a thistle tube with a long stem (C) closed below except for several pin holes, and a conical condenser (D) which rests on the

upper edge of the outer tube. A sufficient amount of glass wool is tied round the lower end of tube C (by means of thread) so that it may serve to impede the upward passage of the ether as it comes from the openings at the end of the tube. Ten c.c. approximately N/10 NaOH solution and 200 c.c. alcohol-free ether are placed in A, and B is then carefully lowered into A by means of the loop of wire. The total fluid in B should not occupy more than three-fourths of the tube. The condenser is put in position and the assembled apparatus placed on an electric heater enclosed in an asbestos box with an opening to fit the lower bulged end of A. The degree of heat is regulated so that the condensed ether drops from the tip of the condenser in an almost continuous stream into the thistle funnel.

The ether used must be free of all traces of alcohol. For the purpose of purifying it commercial ether is shaken several times in a separator with 60 per cent KOH, then washed with water till the washings are neutral, and placed over $CaCl_2$ for a day or so, and finally distilled. This purification is unnecessary when the ether distilled off from previous extractions is used.

When extraction is complete, B is partly removed from A by the wire loop, and C slowly lifted out, allowing every drop of ether to drip from it. The remaining ether in B is caused to overflow into A by cautiously adding water. The contents of A, which should be alkaline, are now carefully transferred to an Erlenmeyer flask connected with a condenser. The flask is placed on a water-bath heated by an electric lamp, the temperature of the water-bath during distillation never being allowed to rise above 50° C. Distillation is continued until no more ether distills over. The flask containing the faintly alkaline water solution of lactate is placed for a few minutes on a boiling water-bath so as to remove all traces of ether, after which the contents are carefully transferred to a one litre fractional distillation flask, being washed into this by means of 300 c.c. of solution (0.5 per cent) of H_2SO_4. The mouth of the flask is then closed with a rubber stopper through which passes the tube of a stoppered funnel, the lower end of the tube being drawn out to a fine point which extends close to the bottom of the flask. This funnel and tube are filled with potassium permanganate solution by suction, care being taken that no air bubbles remain in the tube. The side tube of the flask is so arranged that it can readily be connected with a worm condenser to the delivery end of which is attached a tube which pierces a large rubber stopper fitting a cylinder of about 400 c.c. capacity. This cylinder stands in a vessel of cold water, and to it is added 10 c.c. of approximately N/5 $KHSO_3$ solution (1.2 grams per 100 c.c.) and 10 c.c. of distilled water. The condenser tube is connected with a glass tube which dips into the bisulphite solution. A trap containnig a few c.c. of water is inserted through a second hole in the stopper.

The contents of the distillation flask are now heated, and when boiling commences and steam emerges from the end of the side tube, connection is made between the side tube and the upper end of the condenser. The tap controlling the flow of the permanganate solution is now turned so that the permanganate solution flows at such a rate that the pink color of the solution emerging from the fine point of the tube disappears before reaching the surface of the solution

in the flask. The flame under the flask is now turned down slightly, so that it may be increased in case of back suction. We have found it most important to start the flow of permanganate very slowly, as otherwise the solution changes color too rapidly, and lactic acid is lost. The permanganate is added until a permanent pink (brownish) remains throughout the solution. The tap is then closed and boiling continued for ten minutes more. If no change takes place in the color, oxidation is complete. If otherwise, more permanganate must be added. When oxidation is complete, the side arm is disconnected from the condenser (before turning out the flame).

The condenser and trap are washed into the cylinder with distilled water by means of a water bottle, and the contents titrated against standard iodine (about N/10), starch solution being used as an indicator. It is also necessary with each fresh batch of ether to evaporate the amount (200 c.c.) used for extraction and to oxidize the residue in the flask exactly as in the estimation itself. This blank usually yields a small amount of distillate capable of combining with the bisulphite, but it should never exceed 1 c.c. N/25 iodine solution.

THE TITRATIONS

The following solutions are necessary:

1. *Deci-normal sodium thiosulphate* 24.8 gms ($Na_2S_2O_3$, $5H_2O$) per litre. This is titrated against N/10 potassium dichromate which can readily be prepared by direct weighing from the fused salt. For this purpose about 6 gms. C.P. potassium dichromate is gently heated in a porcelain dish so that it becomes fused. The fused salt is then quickly powdered in a thoroughly dry mortar and placed in a desiccator, 4.913 grams are accurately weighed out and dissolved in 1 litre. To titrate the thiosulphate, 25 c.c. of N/10 dichromate are placed in a stoppered flask, about 2 gms. Pot. Iodide added and then about 5 c.c. C.P. HCl. The bottle is stoppered and allowed to stand for about 10 minutes in a warm place after which it is cooled. The stopper is removed and washed with water into the bottle. The thiosulphate solution is then run from a burette into the bottle until the brown color due to free I. is almost discharged. A few drops of starch solution are added and the titration continued until the blue color is completely discharged. The exact amount of thiosulphate is noted and the normality factor calculated.

2. *Approximately N/25th I-solution*—5 gm. I are placed in a litre flask. Fifteen gms. potassium iodide are dissolved in 200 c.c. water and this solution added to the flask which is then shaken until the I. dissolves. The volume is then made up to 1 litre.

3. *Potassium Bisulphite solution.* Dissolve 1.2 gms. Pot. Bisulphite in 100 c.c. water. This solution should be freshly prepared every two or three days.

4. *Approximately N/10 Potassium Permanganate.* (3.16 gms. per litre.) This is a stock solution from which the solution to be used for oxidizing is prepared. When large amounts of lactic acid are expected a N/100 solution is used. For smaller amounts, as in blood a N/300 is used (i.e. 100 c.c. N/10 stock solution diluted to 3 litres).

5. *Sulphuric acid solution.* 5.0 c.c. H_2SO_4 (con.) in 1 litre water.

6. *One per cent starch solution (soluble starch).*

The routine of an analysis is as follows:

1. Titrate Thiosulphate solution with dichromate. (This need not be done every day.)
2. Titrate 10 c.c. I-solution with Thiosulphate.
3. Titrate 10 c.c. Bisulphite solution against I. (In both these titrations the brown color of the iodine serves as an indicator until near the end point when starch solution is used.)
4. Place 10 c.c. Bisulphite solution in receiving flask of oxidizing apparatus and proceed with oxidation as described on p. 636.
5. Remove flask and titrate distillate with I-solution.
6. Repeat 4 and 5 with ether residue as described on p. 638.

7. The difference between titrations 3 and 5 gives the number of cubic centimetres of I-solution which corresponds to the bisulphite that has combined with the aldehyde liberated by oxidation from lactic acid. The normality of this amount of I. is readily determined from titration 2 (by multiplying it by the value found in 2).

The calculations are as follows:

Each c.cm. N/10 Iodine solution corresponds to 0.5 c.c. N/10 Lactic acid. Therefore if we multiply the value found in the paragraph 7 above by 4.5 it will give the milligrams of lactic acid that have been oxidized. Since the titre of the I. against Thiosulphate solution remains tolerably constant from day to day, it is convenient to use a factor which consists of 4.5 multiplied by the c.c. N/10 Thiosulphate required to combine with 10 c.c. I-solution. This factor multiplied by the difference between the titrations 3 and 5 above gives mg. lactic acid.

To calculate the percentage it is then necessary to allow for the amount of blood and aliquot of filtrate used. The following is an example: Blood used 36.6 c.c.

Aliquot of filtrate used 178 c.c.

(1) 25 c.c. N/10 Dichromate solution = 25.3 c.c. Thiosulphate.
$\therefore$ Normality factor for Thio. = 0.988 (0.99).
(2) 10 c.c. I-solution = 3.7 c.c. N/10 Thiosulphate.
(3) 10 c.c. Bisulphite = 26.7 c.c. I-solution.
(5) After distillation = 14.5 c.c. I-solution.
Difference 12.2
(6) Blank for ether .5
11.7

The equation is: $$\frac{11.7 \times 3.7 \times 0.0045 \times 236.6 \times 10 \times 100}{178 \times 36.6} = 0.0707 \text{ per cent.}$$

The following tests have been made of the degree of accuracy of the method.

There are at least four stages in the process as outlined above at which losses of lactic acid may occur, (a) in the removal of the proteins from the blood, (b) in the evaporation to small bulk of the protein-free filtrate, (c) in the ether extraction (d) in the oxidation of the lactic acid contained in the final extract.

The first to consider is the oxidation process. It has been pointed out by von Fürth and Charnass that the concentration of the permanganate solution must not exceed 0.01 N. Using this strength these workers succeeded in recovering with tolerable constancy 92 per cent of lactic acid from lithium lactate. By no modification of the apparatus or strength of reagents could they obtain greater yields, and if the permanganate solution were made decidedly stronger, these became less satisfactory. On various occasions during the past few years we have had occasion to test this stage of the process and have found that although yields of approximately 92 per cent are certain when considerable quantities of lactic acid are oxidized by means of 0.01 N permanganate; this is not the case when small quantities are uesd.* This is shown in Table I.

TABLE I

LACTIC ACID USED (AS LITHIUM LACTATE)	LACTIC ACID RECOVERED (AS ALDEHYDE)	PERCENTAGE OF LACTIC ACID RECOVERED
0.191 gms.	0.174	91.1
0.099	0.083	82.9
0.0706	0.0593	84.0
0.0202	0.0169	83.6

On the other hand when N/200 to N/300 permanganate is used, and care is taken that the fluid in the oxidation flask does not become tinted pink throughout, equally satisfactory results are obtained with very small amounts of lactic acid (Table II).

TABLE II

LACTIC ACID USED (AS LITHIUM LACTATE) (GM.)	LACTIC ACID RECOVERED (AS ALDEHYDE) (GM)	PERCENTAGE OF LACTIC ACID RECOVERED (PER CENT)
0.01935	0.01755	90.7
0.0125	0.0114	91.2
0.0127	0.0112	88.1
0.0244	0.0224	91.6
0.0155	0.0142	90.1
0.0155	0.0142	90.1
0.0155 (after solution stood 16 hours)	0.0138	89.3

Concerning the *ether extraction* by the Dunbar apparatus, we have found that if this is continued for forty-eight hours with the ether dropping in an almost continuous stream from the condenser, the lactic acid is satisfactorily extracted. It is important, however, to see that a sufficient layer of ether forms on the top of the inner tube, so that none of the underlying watery solution is carried over into the outer tube. Sometimes large bubbles of ether vapor form at the tip of the delivery tube of the funnel, and by passing through the solu-

*The lithium lactate used in these observations was prepared by saturating a solution of lactic acid with zinc carbonate (75 gm. $ZnCO_3$ per 100 gm. lactic acid BP or USP) at boiling temperature, filtering and collecting the crystals of zinc lactate on a Buchner funnel. After recrystallization, the crystals were dissolved in water, the solution boiled and lithium carbonate added in small quantities at a time until a filtered portion of the mixture gave no cloudinesss with H_2S. The mixture was then filtered and the filtrate concentrated until lithium lactate began to separate out, when it was cooled and the crystals separated by suction and dried in a vacuum desiccator. The lithium in the crystals was determined as $LiSO_4$ by cautious incineration in a weighted crucible, a drop of H_2SO_4 (con.) being added after most of the organic matter had been burned off.

tion in the inner tube so agitate it that some of this is inevitably carried over the edge of the tube. When this happens, the perforations in the delivery tube should be made larger. In the following observations quantities of lithium lactate of known strength were extracted, the ether evaporated off and the residues then oxidized as above described.

TABLE III

LACTIC ACID USED (AS LI. LACT.) (GM)	LACTIC ACID RECOVERED (AS ALDEHYDE) (GM)	PER CENT RECOVERED	TIME EXTRACTION HOURS
0.0225	0.0230	excess	46
0.0261	0.0236	90.4	48
0.0266	0.0231	86.7	96
0.0406	0.0370	91.2	72
0.0525	0.0475	85.2	72
0.0244	0.0224	91.6	46
0.0237	0.0194	81.8	72
0.0990	0.0890	90.	55

Although more observations are necessary to make it certain that forty-eight hours is sufficient time for tolerably complete ether extraction, we have chosen this period since we have not found that any greater yield of lactic acid is obtained by longer extraction.

The most serious losses are incurred in *the process of evaporation* of the blood filtrates. Although these are carefully kept at faintly acid reaction, and the temperature never permitted to rise above 40° C., some loss seems unavoidable and unfortunately one cannot be certain of its exact magnitude. Nor can this error be obviated by making the filtrates faintly alkaline, because of the sugar which they contain.

The following observations will illustrate the extent of the losses due to this cause, 50 c.c. of a solution of lithium lactate in distilled water was allowed to stand at room temperature, and at the periods indicated 10 c.c. portions were oxidized.

11:20 A.M.	10 c.c.	contained	.0150	gm.	lactic	acid
2:20 P.M.	"	"	.0142	"	"	"
4:20 P.M.	"	"	.0142	"	"	"
10:00 A.M.	"	"	.0138	"	"	"

This observation was repeated, except that the solution of lithium lactate was dissolved in N/10 HCl with the following results:

10:20 A.M.	10 c.c.	contained	.0243	gm.	lactic	acid
3:15 P.M.	"	"	.0239	"	"	"
10:00 A.M.	"	"	.0229	"	"	"

A distinct decrease is observed in the amount of lactic acid in both cases. We have not determined to what extent this diminution in the amount of recoverable lactic acid would go after prolonged standing in acid solutions, but we have frequently observed that solutions in distilled water show marked deterioration in yield after standing some weeks. Thus, 3 c.c. of a solution of li. lact. made in November, 1921, contained 0.01775 gm. lactic acid, and in Jan., 1922, only 0.0120 gm.

In view of this deterioration, the cause for which we have not investigated, we have always used, for purposes of testing the accuracy of the method, freshly prepared solutions of lactate made up from li. lactate kept in a desiccator.

These losses become still greater when the solutions have to be evaporated, even although the temperature may not be allowed to rise above 30° C.

Quantities of lithium lactate were dissolved in about 200 c.c. distilled water (corresponding to the volume of blood filtrate usually employed), made faintly acid, evaporated in the air current to a volume of 50 c.c., then transferred to the oxidation flask and oxidized with permanganate.

TABLE IV

CONDITION OF LACTATE SOLUTION	AMOUNT LACTIC ACID PRESENT TO START (AS LI. LACTATE)	AMOUNT OF LACTATE ACID RECOVERED (AS ALDEHYDE)	PERCENTAGE RECOVERED
Distilled water	0.0529	0.0379	72
Distilled water	0.0286	0.0235	82.2
Faintly acid	0.0276	0.0223	81
Faintly alkaline	0.0328	0.0265	80.7
Distilled water	0.0300	0.0236	79
Decidedly acid	0.0200	0.0140	70
Decidedly acid	0.0399	0.0282	70.6
Distilled water	0.0197	0.0181	83.2
Faint acid with phosphate buffer	0.0278	0.0247	88.8
Solution of phosphate buffer	0.0155	0.0121	84.7

A part of these considerable losses in the evaporation process may be due to mechanical causes, although we have used every precaution to avoid this. The employment of a buffer mixture of phosphates seems to minimize them and we regret that this precaution had not been adopted earlier in our work.

Realizing that with every precaution, and with precise standardization of the quantities of reagents used, the method is nevertheless fraught with many sources of error, we have from time to time tested its degree of accuracy by adding li. lactate to blood. This test involves an estimation of the lactic acid originally present in one sample of blood and that in another sample to which li. lactate has been added. Some of the more recent results are shown in Table V.

TABLE V

	LACTIC ACID PRESENT IN ORIGINAL BLOOD (PER CENT)	LACTIC ACID ADDED (PER CENT)	LACTIC ACID RECOVERED (PER CENT)	DIFFERENCE BETWEEN 1 AND 3	PER CENT OF ADDED LACTIC ACID RECOVERED
	1	2	3	4	
74	0.087	0.031	0.116	0.029	93
75	0.087	0.116	0.186	0.099	85.3
31	0.062	0.129	0.175	0.113	87.0

THE THERAPEUTIC USE OF GERMANIUM DIOXIDE IN ANEMIA*

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THE erythropoietic action of germanium was first demonstrated by Hammett, Nowrey and Müller,[1] who showed that after subcutaneous injections of germanium dioxide solution into mature albino rats, there was a prompt and marked rise of 1 to nearly 5 million erythrocytes per cu. mm. of the rats' blood. No leucemia was produced as an accompaniment of the erythrocytosis. A similar effect in the guinea pig, rabbit, dog and man was demonstrated by Müller and Iszard,[2] who noted a certain periodicity in the erythrocyte curves. The close chemical relationship between arsenic and germanium in the periodic system originally suggested to these investigators the possibility that germanium might have some effect on erythrocyte formation, a possibility which appears to be substantiated by their findings.

It was shown that the germanium does not accumulate, but is eliminated chiefly through the kidneys and in small part by the alimentary tract.[2] Up to 180 mg. germanium dioxide per kilo body weight, may be given to the albino rat with no apparent harmful results.[3] However, relatively large doses were found to be distinctly toxic to guinea pigs, the lethal dose being about 586 mg. germanium dioxide per kilo body weight. This toxic action may possibly be due to an overstimulation of the blood forming organs.[2] The source of the erythrocytosis appears to be an increased production of red cell precursors in the bone marrow stimulated to greater activity by the germanium.[4]

As a result of these observations it has been suggested that germanium may prove to be a therapeutic agent of considerable value in the treatment of anemia. The subject is one that has aroused considerable interest, although no clinical studies have as yet been reported. The present paper shows the results we have obtained on a series of unselected cases of various types of anemia.

ADMINISTRATION

We have treated sixteen patients suffering from anemia, administering the germanium by mouth in 0.2 per cent water solution. In order to dissolve the germanium dioxide (N. J. Zinc Co. product) it was found necessary to boil the solution for several minutes; the oxide does not precipitate out on cooling. Doses between 100 and 200 mg. of the oxide were given daily or every 2 or 3

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days until about 1 gram had been given. The actual amounts administered may be seen in the table.

METHODS EMPLOYED

Erythrocyte counts were generally made daily during the period of germanium treatment, and for some time afterwards, with counts every few days or weekly later on. Blood counting pipettes and hemacytometer with the double Neubauer ruling, certified by the U. S. Bureau of Standards, were used. Hemoglobin determinations were made by treatment of the blood with 0.1 N hydrochloric acid, allowing it to stand for several hours (Robscheit[5]) to form acid hematin, and comparing against a standard in a Bock-Benedict colorimeter. The standard of acid hematin was prepared from blood whose oxygen capacity was determined by the method of Van Slyke.[6]

The percentage of total solids in the blood was determined[7] to see whether an observed increase in erythrocyte count was real, from an increased production of cells, or only apparent, due to concentration of the blood by decrease in plasma volume, caused by loss of fluid from the blood. If an increase of 25 per cent noted in the red cell count is only apparent, due to decrease in plasma volume, there should be a corresponding increase in the total solid content of the blood. Since finger blood was used and a number of determinations were made, the amount of blood available for total solids, generally less than 100 mg., was not so large as is desirable. Determinations of the leucocyte and differential white cell counts were made several times on most of the patients, while the coagulation time of the blood was determined in several instances. The Wassermann test was done in certain cases before and after the treatment with germanium dioxide. Routine urine analyses, and chemical blood determinations of the urea, uric acid, sugar and chlorides were made before and after the germanium treatment, on certain patients, to determine whether the medication had any harmful effect on the functional efficiency of the kidneys.

DISCUSSION

The data on red cell counts, hemoglobin and total solids in blood are given in the table. The amounts of these constituents in the blood are shown, as well as the percentage of change from the average of several counts made before the germanium was given. The increases in total solids generally run parallel to the hemoglobin changes, but are not sufficiently great to explain the large increases in erythrocytes on the grounds of decrease in plasma volume. In view of the histological findings of Hammett,[4] who showed that many more nucleated erythrocytes were present in the bone marrow of the germanium treated rats, than in the marrow sections of the controls, and that the blood of the test rats contained more young red cells than did the blood of the controls, we feel that our data on total solids strengthen their conclusion that germanium dioxide produces a real erythrocytosis.

The results of germanium treatment on these patients are presented for the purpose of stimulating further study of the problem, and with no attempt to draw general conclusions as to the therapeutic value of the compound, since the number of cases we have studied is so small.

TABLE I

EFFECT OF GERMANIUM DIOXIDE ON THE BLOOD IN ANEMIA

CASE	DATE 1922	GERMANIUM DIOXIDE MG.	BLOOD					
			ERYTHROCYTES		HEMOGLOBIN		TOTAL SOLIDS	
			Million per cu. mm.	Percentage increase	Gms. per 100 c.c.†	Percentage increase	Gms. per 100 c.c.	Percentage increase
1. S. L.	4-12*	100	3.50		11.2		14.7	
	4-14	100	3.86	13	12.1	7	18.0	20
	4-17	150	3.81	12	14.4	28	20.0	30
	4-19	200	4.35	28	13.6	20		
	4-21	200	4.46	31	14.4	28		
	4-24	150	4.78	40	15.4	36	18.9	26
	4-26	200	4.62	36	15.2	35	20.2	35
	4-28		5.00	47	15.4	36	19.3	29
	5-1		5.18	52	14.8	31	19.8	32
	5-5*		5.74	68	17.3	53	21.4	43
	5-8		5.26	54	17.1	51	21.6	44
	5-15		6.05	77	15.9	40	19.7	31
	6-2*		5.90	73	19.4	72		
	6-11		6.09	79	19.4	72		
2. C. B.	4-14*	100	2.02		7.0		13.2	
	4-15	100	2.43	15	7.9	12		
	4-16	100						
	4-17	100	2.18	3	7.9	12		
	4-18	150	2.33	10	7.4	4		
	4-19	150	2.32	10	7.9	12		
	4-20	200	2.70	28	8.0	13	15.7	19
	4-21	200	2.48	17	8.1	15	15.0	14
	4-22	200	2.46	17	8.1	15		
	4-25*		3.09	46	8.2	16		
	5-1*		3.62	71	9.5	35		
	5-16*		3.33	58	8.7	24		
	5-19	200	3.78	79	8.8	25		
	5-20	200			8.3			
	5-21	200						
	5-22	200	3.69	75		17	15.2	13
	5-24	200	3.46	64				
	5-29		3.89	85	9.3	32	16.0	21
	6-1		3.93	86	8.5	21	16.8	27
	6-9		3.64	73	8.5	21	14.3	8
3. I. S.	5-16*	150	4.57		10.2		17.2	
	5-17	150						
	5-18	150						
	5-23	150	4.73	4	10.0	—2	15.4	—10
	5-24	150						
	5-25	150						
	6-7	150	4.94	8	11.0	8		
	6-14		4.59	0.5	11.1	9	17.7	3
4. F. D.	4-1*	100	2.98		9.0		13.0	
	4-2	100	3.49	18	8.8	—3	11.5	—12
	4-3	150	3.42	16	9.2	3	13.8	6
	4-4	150	3.17	7	8.9	—2	14.4	11
	4-5	150	3.20	8	8.8	—3	12.5	—4
	4-6	150	3.23	10	8.9	—1		
	4-7	150	3.01	2	8.9	—1		
	4-14*		3.55	20	9.7	8		
	4-28		2.67	—10	6.2	—31		

†The average normal hemoglobin content for women is 15.5 grams, for men, 17 grams, and for children, below 14 grams per 100 c.c. blood.

*To save space, one or more determinations of blood constituents made before this date are omitted from the table.

TABLE I—CONT'D

EFFECT OF GERMANIUM DIOXIDE ON THE BLOOD IN ANEMIA

CASE	DATE 1922	GERMANIUM DIOXIDE MG.	BLOOD					
			ERYTHROCYTES		HEMOGLOBIN		TOTAL SOLIDS	
			Million per cu. mm.	Percentage increase	Gms. per 100 c.c.†	Percentage increase	Gms. per 100 c.c.	Percentage increase
	5-2	200						
	5-3	200						
	5-4	200						
	5-5	200						
	5-6	200	3.66	24	11.7	30		
	5-8	200						
	5-13		4.18	42	14.1	57		
5. S. C.	4-29*	100	4.10		13.6			
	5-1	100	4.17	—4	14.1	—3		
	5-2	150	3.93	—9	15.0	4		
	5-3	150						
	5-4	150	4.58	6	15.9	10		
	5-5	150						
	5-6	100	4.85	12	15.0	4		
	5-8	200	5.34	23	15.2	5		
6. J. S.	6-7*		3.85		10.6			
	6-9	150						
	6-10	150			10.4	—2	18.0	
	6-11	Less than 150						
	6-12	Less than 150	4.59	21	11.5	9	15.9	
	6-14		4.51	19	10.9	3	16.2	
7. J. M.	4-17*	100	3.94		12.8		18.7	
	4-19	100	3.94	—3	12.9	1	16.5	—12
	4-21	150	4.18	3	13.1	2	17.9	—5
	4-24	150	4.26	5	14.1	10	17.7	—6
	4-26	150	4.45	10	13.2	3	18.7	0
	4-28	150	4.70	16	14.1	10	18.0	—4
	5-1	150	4.52	12	13.6	6	18.4	—2
	5-3	200	4.38	8	13.1	2	19.3	3
	5-10*		5.10	26	13.7	7	20.9	12
	5-26		4.06	0.4	13.6	6	18.5	—1
	6-7		4.30	6	12.7	—1	18.1	—3
8. I. N.	3-21*		3.84		6.8		13.2	
	3-22	100						
	3-23	100	4.45	18	7.0	3	12.4	6
	3-24	150	4.86	30	7.2	6	13.2	0
	3-25	150	4.99	33	7.4	9	15.1	14
	3-26	150	4.80	28	7.3	7		
	3-27	150	5.18	38	7.4	9		
	3-28	150	4.70	25	7.1	4	14.3	8
	3-29		5.41	44	7.4	9	13.0	—2
	4-2*		4.83	29	7.4	9	13.4	2
	4-4*		5.76	53	7.8	15	15.8	20
	4-15*		5.18	38	7.6	12	13.6	3
	4-22		4.05	8	7.3	7	14.1	7
	4-29	150	4.32	15	7.4	8	12.9	—2
	5-1	150	4.56	21	7.6	12	14.4	9
	5-3	150	4.15	11	7.0	3	14.5	10
	5-8	150	4.68	25	6.9	2	10.6	—20

†The average normal hemoglobin content for women is 15.5 grams, for men, 17 grams, and for children, below 14 grams per 100 c.c. blood.

*To save space, one or more determinations of blood constituents made before this date are omitted from the table.

TABLE I—CONT'D

EFFECT OF GERMANIUM DIOXIDE ON THE BLOOD IN ANEMIA

CASE	DATE 1922	GERMANIUM DIOXIDE MG.	BLOOD					
			ERYTHROCYTES		HEMOGLOBIN		TOTAL SOLIDS	
			Million per cu. mm.	Percentage increase	Gms. per 100 c.c.†	Percentage increase	Gms. per 100 c.c.	Percentage increase
	5-11	150	4.54	21	6.9	2	13.6	3
	5-15	150	4.43	18	7.2	6		
	5-20*		4.25	13	7.9	16	14.4	9
	5-26*		4.23	13	7.0	4	13.3	1
	6-8*		4.01	7	7.5	10	13.0	—2
	6-13		3.78	0.5	7.5	11	15.0	14
	6-17		3.86	3	7.7	13		
9. W.	5-2	200	4.54		10.1		18.5	
	5-3	200						
	5-4	200						
	5-5	200	4.44	—2	9.5	—6	16.0	—13
	5-6	200						
	5-7	200						
	5-15*		4.22	—7	9.7	—4	19.1	3
	6-9*		4.36	—4	10.2	1	17.5	—5
	6-22		4.44	—2	11.0	9	17.7	—4
10. E. A.	4-13*	100	3.41		8.5		15.5	
	4-15	100	3.46	1	8.0	—5	13.2	—15
	4-17	100	3.32	—3	8.7	3	14.6	—6
	4-19	100	3.59	5	8.7	3	13.3	—14
	5-9		2.63	—23	6.3	—25	13.8	—11
	5-10	100	2.74	—20	6.3	—25		
		Less than						
	5-11	100						
	5-12	100	2.51	—26	5.9	—31	10.4	—33
	5-14	100	2.72	—20	6.3	—25		
	5-15	100						
	5-16		2.08	—39	5.8	—31	11.2	—28
	5-19		1.93	—43	5.2	—39	12.3	—21
	5-21		2.57	—25	5.8	—31		
11. L. M.	6-6*		3.34		9.3			
	6-8	150						
	6-9	150	3.30	0	9.3	1	17.4	
	6-10	150	3.53	7				
	6-11	150						
	6-12	150	3.26	—1	9.8	6	15.1	
	6-13	150						
	6-14	150	3.28	—1	9.3	1	15.3	
	6-21*		3.85	16	10.2	11	16.0	
	6-30		3.35	1	9.4	2	15.9	
12. W. U.	4-13*	100	3.84		14.8		19.4	
	4-14	100	3.71	—7	13.9	—8	18.8	1
	4-15	100	4.01	1	15.0	—1	17.7	—5
	4-16	100						
	4-17	100	3.80	—5	14.8	—2	17.6	—6
	4-18	150	4.22	6	15.0	—1	17.9	—4
	4-19	150	4.15	4	14.4	—5		
	4-20	200	3.99	0	14.6	—3	18.9	1
	4-21	200	4.19	5	13.7	—9	18.9	1
	4-22	200	3.90	—2	13.9	—8		
	5-8*		4.13	4	13.0	—14	19.9	6
	5-16*		3.68	—8	12.8	—16		

†The average normal hemoglobin content for women is 15.5 grams, for men, 17 grams, and for children, below 14 grams per 100 c.c. blood.

*To save space, one or more determinations of blood constituents made before this date are omitted from the table.

TABLE I—CONT'D

EFFECT OF GERMANIUM DIOXIDE ON THE BLOOD IN ANEMIA

CASE	DATE 1922	GERMANIUM DIOXIDE MG.	BLOOD					
			ERYTHROCYTES		HEMOGLOBIN		TOTAL SOLIDS	
			Million per cu. mm.	Percentage increase	Gms. per 100 c.c.†	Percentage increase	Gms. per 100 c.c.	Percentage increase
13. T. P.	6-14		2.11		7.8		13.3	
	6-15	150						
	6-16		2.22	5	7.6	—3	13.5	1
	6-17	150						
	6-18	150						
	6-19	150	2.03	—4	7.9	1	14.8	11
	6-20	150						
	6-21	150	2.16	2	7.5	—4		
	6-22	150						
	6-23	150	2.18	3	7.5	—4	14.5	9
	6-24	150						
	6-30		1.94	—9	7.3	—5	15.5	16
	7-3		1.94	—9	7.8	0	13.5	1
14. W. H.	7-10		2.70		10.4		16.6	
	7-11	150						
	7-12	150	2.37	—12	10.0	—4	14.5	—13
	7-13	150						
	7-14	150	2.52	—7	10.5	1	15.2	—8
	7-15	150						
	7-16	150						
	7-17		2.65	—2	11.2	8		
	7-19	200	2.48	—8	10.7	3	14.4	—13
	7-20	100**						
	7-21	100**						
	7-22	100**			10.4	0	16.5	—1
	7-24		2.40	—11	10.3	—1		
15. A. K.	7-5		2.02		4.6		11.3	
	7-7	25						
	7-8	35	2.05	1				
	7-9	50						
	7-10	50	2.33	15	5.1	10	11.8	5
	7-11	50	2.59	28	5.5	21		
	7-13	50	2.76	37	6.2	35	12.1	7
	7-14	50	2.62	30	6.0	30		
	7-15	50	2.81	39	6.1	32		
	7-16	50						
	7-17		2.75	36	6.1	32		
	7-19	50	3.00	48	6.2	35	11.6	3
	7-22		3.18	57	6.7	46	12.3	9
	7-24		3.21	59	6.6	44		
16. C. F.	7-7*	150	4.22		8.3		16.0	
	7-8	150						
	7-9	150						
	7-10		3.86	—9	8.5	2		
	7-11	100						
	7-12	150	4.52	7	8.7	5	15.4	—4
	7-14	150	4.86	15	9.2	11	14.7	—8
	7-15	150						
	7-17		4.64	10	8.3	0		

†The average normal hemoglobin content for women is 15.5 grams, for men, 17 grams, and for children, below 14 grams per 100 c.c. blood.

*To save space, one or more determinations of blood constituents made before this date are omitted from the table.

**In these instances a 0.2 per cent solution of germanium dioxide in 0.4 per cent sodium bicarbonate solution was used.

In the four cases of anemia following hemorrhage (cases 1-4 in Table) it is seen that the ingestion of the germanium was followed by prompt and large increases in both red cells and hemoglobin. The maximum increases in red cells were 79, 86, 8 and 42 per cent of the control counts, with increases up to 72, 35, 9 and 57 per cent above the control hemoglobins. In these cases there seemed to be little tendency for the counts to decrease to the original level after the effect of the treatment had worn off. While it is well recognized that after hemorrhage there is generally somewhat rapid regeneration of erythrocytes, germanium may prove to be of value in stimulating this regeneration.

CASE 1.—S. L., male; age thirty-five; March 14, 1922, a herniotomy was performed; March 24, hemorrhage from the lower bowel; diet, mixed.

CASE 2.—C. B., male; age twenty-four; weight 125 pounds; April 3, operation on fibrosarcoma of right antrum, hemorrhage at time of operation; diagnosis, fibroma of antrum, nose and nasopharynx; May 31, slight hemorrhage; treatment, May 31, 110 mg. of radium; diet of meat, eggs, milk, vegetables.

CASE 3.—I. S., male; age twenty-four; diagnosis empyema; April 28, resection of part of 6th rib; hemorrhage following operation; diet mixed; at time of germanium treatment patient was still discharging pus from pleural cavity.

CASE 4.—F. D., female; age forty-eight; diagnosis, carcinoma of body of uterus and cervix; October, 1921, hysterectomy was performed; treatment before germanium treatment, 10,000 mg. hours of radium; slight bleeding for some days beginning April 4; April 27, hemorrhage of about 1.5 ounces; treatment, beginning April 19, 1.5 ounces "ovoferrin" daily, and 1/4 gr. morphine daily; diet, soft, with eggs, milk, cereal, toast; death on May 13.

S. C. (Case 5), a woman with secondary anemia, visceroptosis and colitis, responded to the germanium treatment by a maximum increase of 23 per cent in red cells and 10 per cent in hemoglobin.

J. S. (Case 6), a woman who had dental caries, pyorrhea, and chronic arthritis, received four doses of germanium, but vomited part of the last two doses. She showed maximum increases in red cells of 21 per cent and of 9 per cent in hemoglobin. Unfortunately these two patients (5 and 6) were not studied after the treatment ended, and we are unable to tell whether the increase in red cells was permanent.

CASE 5.—S. C., female; age forty-seven; diagnosis visceroptosis, colitis and secondary anemia; diet mixed.

CASE 6.—J. S., female; diagnosis, dental caries, pyorrhea, chronic arthritis and secondary anemia; diet, soft; medication, 75 gr. sodium bicarbonate daily, May 15-20; 30 gr. tolysin daily May 20-June 6. Blaud's pills, 6 daily, May 20-June 6.

J. M. (Case 7), a woman suffering from mucous colitis, tachycardia and secondary anemia, showed response to germanium by increases in red cells up to 26 per cent above the control; 3 weeks after the treatment the red cell count was 0.4 per cent above, and 2 weeks later, 6 per cent above the control. The maximum increase in hemoglobin was 10 per cent; 5 weeks after the treatment it had decreased to 1 per cent below the control.

I. N. (Case 8), a woman with secondary anemia, responded to germanium treatment with maximum increases of 53 per cent in red cells and 15 per cent in hemoglobin; twenty-four days after the last dose, the red cells had dropped to 8 per cent and the hemoglobin to 7 per cent above the original counts. A second treatment resulted in increases of 25 per cent in red cells and 16 per cent in hemoglobin; a month after this treatment the red cell count had decreased to 0.5 per cent, with a rise 4 days later to 3 per cent above the control. The hemoglobin at this time was 13 per cent above the control; a month earlier the patient had begun taking 1.5 ounces of "ovoferrin" daily, which may explain the fact that the hemoglobin remained at a higher level than the cells. The cause of the anemia in this case was unknown although there was a possibility of congenital syphilis.

In Cases 7 and 8 it appears that if the cause of the secondary anemia is not removed, the effect on the blood count of treatment with germanium may be relatively transitory. This type of secondary anemia, particularly, warrants further study with germanium.

CASE 7.—J. M., female, age thirty-five; diagnosis, mucous colitis, tachycardia and secondary anemia; diet, mixed.

CASE 8.—I. N., female; age nineteen; weight 114 pounds; diagnosis, secondary anemia, cause not determined, possibly congenital syphilis; blood Wassermann negative; diet, soft, with vegetables, meat and eggs; medication, beginning May 15, 1.5 ounces "ovoferrin" daily; June 13, teeth x-rayed; June 15, several teeth extracted, of which 3 were abscessed.

A woman, W., (Case 9), with carcinoma of the cervix, who was given germanium one week after the last radium treatment, showed decreases in both red cells and hemoglobin. The toxemia due to carcinoma, or the radium treatment may have counteracted the effect of the germanium in this case.

E. A. (Case 10), a girl with malignant endocarditis, streptococcus viridans type, showed small increases in red cells and hemoglobin after the first germanium treatment, but later, due to the progress of the disease, the counts had dropped decidedly, and a second treatment with germanium had little influence on the blood picture.

In the case of L. M. (Case 11), a girl suffering from malignant endocarditis, streptococcus viridans type, there were moderate increases and decreases in erythrocytes after germanium, with a maximum increase of 11 per cent in hemoglobin; a week after this the hemoglobin was 2 per cent above the control.

W. U. (Case 12) a man suffering from chronic cardiovalvular disease, reacted to germanium treatment with small increases and decreases in red cells, and decreases as great as 16 per cent below the control hemoglobin content.

T. P. (Case 13), a man suffering from pernicious anemia showed small increases and decreases in both erythrocytes and hemoglobin following germanium ingestion.

The treatment of a second case (W. H. 14) of pernicious anemia with germanium resulted in decreases in red cells, with small increases and decreases in hemoglobin.

Judging from the blood counts, Cases 9-14 showed practically no improve-

ment following germanium administration. Clinically there was little, if any, improvement. These are rather unfavorable cases, however, by which to judge any treatment, since the anemia was caused by pathological conditions which are difficult to remedy.

CASE 9.—W., female; age forty; diagnosis, carcinoma of uterus, cervix and anterior vaginal wall; treatment, 10,000 mg. hours of radium, last application on April 24; beginning May 8, 1.5 ounces "ovoferrin" daily; diet mixed.

CASE 10.—E. A., female; age thirteen; weight 70 pounds; diagnosis malignant endocarditis, streptococcus viridans type; diet, high caloric, and after June 9, soft.

CASE 11.—L. M., female; age twenty-one; diagnosis, malignant endocarditis, streptococcus viridans type; diet, high caloric; medication, 20 gr. tolysin daily, May 8-June 1; Blaud's pills, 6 daily, June 1 to 6; Fowler's solution, 9 minims daily, June 1-6.

CASE 12.—W. U., male; age forty-five; weight 107 pounds; diagnosis, chronic cardiovalvular disease, aortic regurgitation, mitral stenosis and regurgitation, myocardial insufficiency; diet, soft; medication, April 10-May 22, 45 minims tincture of digitalis daily.

CASE 13.—T. P., male; age fifty-three; weight 140 pounds; diagnosis, pernicious anemia; diet, high caloric; blood Wassermann negative, spinal fluid Wassermann positive; medication, neosalvarsan, 0.2 gm. May 22, 0.3 gm. May 29, 0.45 gm. June 5, 0.6 gm. June 12, 0.9 gm. June 20; mercuric chloride 1 gr. April 28, May 8, May 19; transfusion of 520 c.c. blood April 22, 560 c.c. May 3, 580 c.c. June 2.

CASE 14.—W. H., male; age fifty-six; diagnosis, pernicious anemia; five transfusions between September, 1921 and April, 1922; diet, mixed.

A. K. (Case 15), a boy aged 1½ years, who was convalescing from lobar pneumonia and parotitis, responded to treatment by prompt increases in red cells up to 59 per cent and in hemoglobin up to 46 per cent above the control.

C. F. (Case 16), a woman suffering from hemorrhoids, gave response to treatment by increases of 15 per cent in red cells and 11 per cent in hemoglobin. The effect of the germanium was somewhat influenced by slight bleeding.

CASE 15.—A. K., male; age one and one-half years; weight, 20 pounds; diagnosis, anemia, convalescence after lobar pneumonia and parotitis; diet, milk, vegetables, cereals, broth, bread.

CASE 16.—C. F., female; age thirty-two; diagnosis, hemorrhoids, internal, with slough, hemorrhoidectomy, July 18; diet, mixed.

By a study of the table it is seen that the periodic rise and fall of the red cell count after germanium, noted by Hammett and Müller, was also seen in this series of cases. The hemoglobin generally showed less of this periodic effect. The influence of germanium on hemoglobin production was usually somewhat less marked and more delayed than its influence on red cell formation; consequently, the color index usually dropped slightly early in the treatment and rose later.

Determinations of the coagulation time of the blood were made in 5 cases before and after the treatment, and revealed no noteworthy effect due to the germanium. There was no significant change in the white blood cell counts, nor in the distribution of different forms of white cells as shown by differential counts of the stained blood smears. From the results of the Wassermann test done in 4 cases before and after the treatment, it appears that the germanium did not affect the reaction of the blood to the test. A study of chemical blood

and urine analyses in 7 cases revealed no apparent effect of the germanium on the functional activity of the kidneys.

CONCLUSIONS

The influence of germanium dioxide on red blood cell formation has been studied in sixteen cases of anemia—four cases of anemia following hemorrhage, ten cases of secondary anemia and two cases of pernicious anemia. In some of these cases the germanium was found to have distinct erythropoietic action. Whether this property shall prove to be of great therapeutic value in the treatment of the anemias remains to be shown by further careful study of more cases than are here presented.

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THE RELATION OF ACHYLIA GASTRICA TO CHRONIC FOCAL INFECTIONS AND PERNICIOUS ANEMIA*

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THE high mortality of pernicious anemia warrants the presentation of any data which might enable a diagnosis of the latter disease to be made earlier or even suspect its oncoming. It is this motive which actuates the report of three cases of long continued focal infections passing through the stages of achylia gastrica, pernicious anemia, and death. The sequence of events whereby achylia gastrica preceded pernicious anemia in a chronological order in no way determines the former as an etiological factor of the latter, but it is the purpose of the writer in this connection to point out this possible relationship. The association of these two conditions has attracted the attention of clinicians for many years and efforts have been made to place the two conditions in the light of cause and effect. This attempt has not been successful and a careful analysis of all the data does not lead to the conclusion that such a relationship is at all probable.

Achylia gastrica is not a rare condition. It is a rather common finding and would be even more common were the gastric contents of patients routinely examined. The loss of gastric secretion may be complete or partial. Achylia may be associated with direct atrophy of the glands of the mucous

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membranes of the stomach or it may result from a depression of the function of the glands due to a large number of causes. It is associated with many toxic conditions, infections, nervous states, and vascular disturbances. It is stated by careful observers that total and persistent gastric achylia is consistent with perfect health and well being. However, such a condition must be unusual in comparison with the large number of cases associated with definite predisposing causes.

Fenwick reported the association of achylia gastrica and pernicious anemia as early as 1880 and since that day a voluminous literature has appeared. There has been a great diversity of opinion in regard to the relationship between this glandular degeneration or depression of function and the blood changes so that the question of cause and effect has been brought up. Many writers have considered the glandular degeneration as the primary factor and it is true that total atrophy of the gastric glands may cause serious disturbances of the general health. On the other hand, there is no question that complete loss of peptic power may be tolerated for many years without apparent impairment of the general health providing that the motor power of the stomach remains good, permitting the intestine to assume more or less vicariously the functions of the stomach.

Large numbers of cases of pernicious anemia have been subjected to gastric analysis in the earlier stages and it has been shown that the gastric mucous membrane is not always involved at this time, but as the disease advances and the anemia increases there is usually a corresponding decrease in the secretions of the stomach so achylia is nearly always present sooner or later. Comparatively little attention has been directed to the clinical fact that achylia gastrica may precede anemia in some cases for long periods of time. No importance is to be given to this association of events if it is assumed that these conditions are altogether separate and occur only as coincidental events. In fact, Stockton, editing Nothnagel's System of Medicine, states that when achylia precedes the pernicious anemia it is to be considered as coincidental. Exception may be taken to this on very definite grounds. There is reason to believe that the two conditions are manifestations of the same causative factors. It is not my purpose here to discuss the various agents assumed to be predisposing factors in the development of pernicious anemia. There is, however, an impression more or less general that pernicious anemia is a result of some infection in the body continuing over long periods of time, possibly for many years, so that the blood forming organs are damaged and rendered incapable of forming new cells. The fact that achylia gastrica may be due to similar states or infections in the body, whether in the tonsils, teeth, sinuses, gall bladder, prostate, or other places, has not been sufficiently emphasized.

Achylia gastrica is assumed in this connection to mean a condition of absent hydrochloric acid, as shown by congo red, with a total acidity that is very low or altogether absent. The gastric secretion is very susceptible to chronic infections of the body of whatsoever nature. It is absent in many conditions of the most diverse nature. My purpose in reporting three cases

of pernicious anemia which have been preceded by achylia gastrica for long intervals of time is not to insist that such a relationship is constant, but that when achylia is found in the presence of such infections it may be considered as a warning signal of a possibly oncoming pernicious anemia. The recognition of pernicious anemia in the stage of its incipiency or in a stage before it is considered pernicious is of absolute importance in consideration of the hopeless prognosis in this disease. Despite the use of blood transfusions and other known therapeutic resources, the ultimate results in pernicious anemia are so uniform that any recognition or warning of the incipient stage of this condition is worth serious consideration. It is a relatively easy matter to determine the chemistry of the gastric contents, especially since the general use of the small duodenal tube. The use of this tube has made gastric analysis much more common and in view of the ease of introduction, it may be possible to detect these early cases in this way. Given a case of severe infection at the roots of the teeth, sinuses, tonsils, or other places, with slight grades of anemia, gastric analysis should be routinely made if there is any suggestion of digestive disturbances. The presence of an achylia in such a condition should at once throw the clinician on his guard because an infection which is severe enough to inhibit the secretion of the gastric mucosa may be severe enough in its toxic manifestations to result eventually in bone marrow changes with the evidences of a fatal anemia. There is no characteristic syndrome suggestive of achylia. There may be no symptoms whatever or on the contrary the patient may complain markedly. The appetite may be reduced, there may be a marked aversion to meat, fullness of stomach, gas, or occasional paroxysm of pain may occur. These attacks may occur after eating, soon after a meal, soon disappearing or persisting for a considerable period of time. Vomiting occasionally occurs but it is not a constant symptom. It may occur soon after eating and consist of coarse, undigested remnants of food, usually without blood. Headache and vertigo are common. The bowels are often sluggish but diarrhea is common in the later stages and is a characteristic symptom.

Einhorn has called attention to the fact that there are occasional cases of achylia that present symptoms quite parallel to those of hyperacidity. The only way to arrive at a diagnosis is by gastric analysis, which may have to be repeated. William Hunter stated that pernicious anemia should be laid at the door of mouth infection. Pernicious anemia has also been ascribed to some general disturbance of the lipoid functions of the body with a production of abnormal hemolytic substances liberated in undue amounts exerting a destructive influence on the red blood cells.

CASE I.—T. E. H.; age forty-eight; married; merchant; American; first seen in August, 1916.

Patient's Complaint: Comes for examination because of belching after food, gas, vomiting spells, and sick headaches.

Family History: Analysis of the family history does not reveal anything pertinent to the present illness.

Previous History: There have been several attacks of tonsillitis at various periods in his early life. Tonsils were not removed but were submerged and shrunken at the time when

he was first seen. Patient has had pains (rheumatic?) in the knee joints, hips, and shoulders at various intervals throughout the past ten years. These pains were not severe enough to put him in bed but were troublesome and inconvenienced him a great deal. There was a Neisser infection at the age of 24. Patient was treated for typhoid fever four years before he was seen by me. Denies any syphilis.

Habits: Smokes two cigars daily. Does not use cigarettes or pipe. Alcohol is used sparingly. Patient states he is not a heavy eater.

Present Disease: The date of the onset of the present disease is not definite. The belching and gas for which he comes have been coming on more or less gradually and increasing in severity throughout the past four or five years. These symptoms were not troublesome enough at the outset to make him pay much attention to them and they were disregarded more or less. During the past year they have been troublesome enough, especially the belching and vomiting, to make him seek relief from a physician. The patient is troubled also with what he calls "canker sores" in his mouth for the past few weeks. These have also been present at a previous period some months ago. Analysis of the gastrointestinal symptom reveals that his belching and eructations have a rather definite relationship to his eating and are much worse after such foods as fatty substances, fried meats, or gravies. Tea is not well tolerated. There is no definite pain at any time in the abdomen. No jaundice. The appetite is much disturbed and has been so for five or six years back. There are no symptoms referred to the heart or circulatory system. There is no particular trouble with urination excepting that occasionally and at long intervals there is a little difficulty in urination due to an old stricture. Dizziness is an occasional complaint. There has been no appreciable loss of weight.

Examination of the Patient: There is nothing abnormal with respect to the temperature, pulse or respiration. The patient is a medium sized individual, weight 150 (usual 160); the skin has a rather sallow color with perhaps a tinge of yellow; there is no abnormality with respect to the bones, joints, or lymph glands; station and gait are normal; patient is a bit listless but there is no other mental abnormality; there are no skin lesions, no scars, no edema, and no external ulceration. Examination of the throat shows the tonsils rather shrunken and submerged but without visible pus. There are rather numerous small ulcer areas in the mouth the size of a pinhead or a little larger. The teeth looked good but were later found to be abscessed. There is no apparent trouble in the sinuses, nares, or ears. The pupils are equal on the two sides, react to light and in accommodation. The thyroid is not enlarged. The thorax is normal in appearance, and with respect to equality of respiration on the two sides. No abnormal findings can be determined with respect to the lungs, heart, or arterial system. Blood pressure was rather low, 108/60. The abdomen did not show anything unusual on inspection. Palpation was not tender and did not reveal any rigidity, mass, or abnormal splashing sounds. The liver, spleen, and gall bladder could not be palpated. The appendix region was not tender. There were no hemorrhoids. The genitourinary apparatus showed an old gonorrheal stricture. There were no scars on the genitalia indicating any specific lesions. Examination of the nervous system showed the patellar reflexes to be present on both sides; no Babinski; no Romberg; no ataxia; no nystagmus; sensation was normal with respect to touch and pain.

Laboratory Findings: The urine contained a few pus cells, possibly from the old stricture formation, specific gravity 1022, no albumin, no sugar, no blood, acid reaction. The blood examination showed red blood cell count 4,600,000; hemoglobin 90 per cent; white count 9,600; stained specimen showed the following differential count: Polymorphonuclears 68 per cent, small lymphocytes 20 per cent, large mononuclears 9 per cent, eosinophiles 2 per cent, basophiles 1 per cent; no parasites were seen; the red blood cells were well formed; there was no inequality in the size of the erythrocytes; no polychromasia; and no poikilocytosis; the blood Wassermann was negative. The stomach contents removed after an Ewald test breakfast showed no HCl to congo red after 20, 40, or 60 minutes. The total HCl was not more than 2-6 at any time. Lactic acid was absent. The gastric contents showed no blood and no sign of any unusual residue. No sarcinae or Oppler-Boas bacilli.

Two years following the time when this patient was first seen (February, 1918) the blood assumed changes sufficiently marked to enable a diagnosis of pernicious anemia to be made. The red blood cell count gradually decreased, reaching 1,200,000 as its lowest point; the white cells varied from 3,000 to 6,500; the hemoglobin progressively dropped and reached as low as 24 per cent (Dare); the color index was usually over 1 plus. The stained blood smears showed at various times the findings characteristic of pernicious anemia. There was anisocytosis, polychromasia, poikilocytosis, and nucleated red blood cells. This patient was subjected to repeated blood transfusions, medicinal treatment, all the teeth were removed while he was under the care of another physician, and despite everything that could be done the patient died in May, 1921.

CASE II.—Mrs. R. J. S.; age forty-nine; married; housewife; American; patient first seen in July, 1917, on account of persistent soreness in the mouth and gastric distress.

Family History: The parents are both living in good health. One sister died of pulmonary tuberculosis. No other condition determined having any apparent connection with the present illness.

Previous History: Patient had measles and whooping cough when a child. Since the age of twenty-four has had a great deal of trouble with teeth. Several were extracted on account of pyorrhea and those that remained were more or less involved with pyorrhea. She had refused to have all her teeth extracted prior to this time. At the age of thirty-five there was a moderate attack of rheumatism in the right knee with some swelling and redness, keeping patient in bed for several weeks but gradually subsiding. At other times during the past six or seven years there have been vague and more or less obscure pains in both shoulders and the knees, doubtless evidences of a chronic arthritic condition. No venereal disease that could be determined on examination.

Present Illness: Has had a rather insidious onset. For a number of years back she has complained of sores in the mouth coming as small, isolated, very painful ulcers. These would usually heal after a few days with the application of some home remedy. While these sores were present patient would refrain from eating to a considerable extent on account of the pain produced, so that there was more or less loss of weight. The highest weight which the patient reached has been 150 and has gradually declined to 127. Associated with this condition in the past two or three years there has been distress in the stomach region following the use of heavy foods. Could eat soft foods, such as eggs, cereals, and liquids without any distress, but burning in the stomach region and a feeling of weight and discomfort followed the taking of heavier foods more or less constantly. Patient was not able to ascribe the appearance of this trouble to any definite condition as far as she knew. It was not constant and might disappear for relatively short periods. There were no symptoms referable directly to the heart, lungs, or urinary system.

Physical Examination: Shows a rather emaciated woman, weight 127, slender frame. There were no palpable lymph glands. The joints were not enlarged, tender or deformed. Movement of the right shoulder and left knee showed distinct crepitation. The skin did not show any lesions or scars. Examination of the mouth showed two or three small, clearcut, punched out, ulcerated lesions not larger than a grain of wheat. These were surrounded by a small area of reddening; the lesions were very painful to touch. The gums were in bad condition and pus could be pressed out from around several of the teeth. The thorax was well shaped and no disease could be determined with respect to the heart and lungs. The abdomen was retracted and did not show anything unusual on inspection. Dullness over the liver and spleen was not increased and these structures could not be felt on palpation. There was no unusual tenderness over the epigastrium even during the periods when the patient complained of distress here. No increased visible peristalsis. No disease could be determined in the gall bladder or appendix by the usual methods of examination. No disease was found with respect to the genitourinary apparatus.

Laboratory Findings: The urine showed a normal amount secreted in twenty-four hours, specific gravity 1018, acid, no albumin, no sugar, no casts, or other abnormal cellular

elements in the sediment. The blood findings showed red blood cells 4,220,000; white cells 7,600; hemoglobin 92 per cent; differential count: Polymorphonuclear 69 per cent, small lymphocytes 19 per cent, large mononuclear 9 per cent, eosinophiles 2 per cent, mast cells 1 per cent. The gastric contents were removed forty minutes after an Ewald test breakfast and showed no free HCl, total HCl 6, no blood, no lactic acid, and no apparent residue in the stomach.

A diagnosis was made of achylia gastrica and the patient put upon large doses of dilute HCl. She showed marked improvement with respect to the gastric distress following heavy foods and also a prompt improvement in the appearance of the ulcerations in the mouth. At this time the patient refused to have all her teeth extracted, but did visit a dentist and had several of the worst ones removed.

The patient did not gain in weight and was not seen for a period of several months while she remained fairly well. Early in 1918 the patient showed distinct evidences of pernicious anemia with a red count of 1,640,000; white count 3,400; hemoglobin 32 per cent (Dare); color index .99 plus. The stained blood smear showed marked distortion and deformity of the red blood cells, marked inequality of size varying from large macrocytes to very small microcytes. Many of the red blood cells showed nuclei. There was present also at this same time distinct evidences of involvement of the spinal cord. There was moderate ataxia, marked paresthesia around the trunk and back, constricting pains around the abdomen, and pains in the shoulder. The patellars were 1 plus; no Babinski; Romberg 2 plus; pupils equal on two sides and react promptly to light. The blood Wassermann at this time was negative (twice). The spinal fluid examination showed a clear fluid, 3 cells per c.mm., globulin not increased, no organisms seen in the stained smear, spinal fluid Wassermann negative in amounts up to 1.5 c.c.

At this time the patient consented to have all her teeth removed showing large amounts of pus at the roots. The anemia persisted despite the ordinary methods of treatment, including two citrated blood transfusions of 500 c.c. each. The patient died after three months with evidences of very advanced anemia with marked cord involvement.

CASE III.—L. F.; age fifty-six; married; merchant; first seen June, 1916.

Patient's Complaint: When this patient was first seen, his chief complaint was distress and pain in the upper abdomen between the epigastrium and the umbilicus. This pain usually followed the taking of food but there was no constant relationship. There was no relationship to the amount of pain as light meals or light foods would be followed by distress in the same way as heavy meals.

Family History: There is nothing unusual in the family history which would have any bearing on the present trouble. The parents and the relatives, in the main, have reached advanced ages.

Previous History: There is a very definite history of rheumatic pains or lumbago about twenty-five years ago. Has been confined to sanitariums at intervals for this condition. There is no definite history of attacks of tonsillitis but has complained frequently of sore throat. The tonsils have never been removed. There is no history of any venereal disease. Patient has always worked fairly hard in his business and has eaten fairly well. Alcohol is used moderately, also six or seven cigars daily.

Present Complaint: Dates back two or three years. It is not possible to place a precise or definite time limit on the beginning of his trouble because the onset is rather insidious. In addition to the digestive disturbances mentioned above, the patient has noticed a distinct sense of weakness or fatigue. He is not able to do his work well. Has to rest frequently and thinks that his efficiency is distinctly below par.

Examination at this time showed a moderately well developed man. Weight 154. Looks rather pale with a slightly pasty complexion. No enlarged glands could be palpated. The joints and bones did not show any definite disease to external examination. Skin rather sallow, no skin lesions or scars. The teeth showed a considerable amount of repair work and there are evidences at the gums of infection. The tonsils were somewhat submerged

but did not exude any pus on retraction of the pillars. The tongue was not unusually red. There are no ulcers in the mouth or evidence of stomatitis. Thyroid not large or palpable. The thorax is fair size showing a fairly equal expansion on the two sides. No disease was found with reference to the pulmonary system. The heart did not show anything unusual excepting a very soft systolic bruit heard in the fourth and fifth left interspace in the mid-clavicular line and not being transmitted well. The blood pressure is 135/60. The abdomen was rather retracted and did not show anything on inspection. The liver and spleen could not be palpated. Deep pressure did not elicit any pain over region of gall bladder or appendix. The rectal muscles were not rigid. There was no disease to be determined with respect to the genitourinary apparatus. The urine showed specific gravity 1,018, no albumin, no sugar, no blood, and one or two pale hyalin casts in the centrifuged specimen. The blood examination at this time (June, 1916) showed hemoglobin 88 per cent, red blood count 4,600,000, white count 6,500, differential count: Polymorphonuclears 72 per cent, small lymphocytes 21 per cent, eosinophiles 1 per cent, mast cells 1 per cent, large mononuclears 5 per cent. There was no evidence of any change in the size of the red blood cells no nucleated red blood cells seen, and no difference in the staining power. The gastric analysis showed at this time an entire absence of HCl both free and combined. Tests for pepsin were not made. There was no blood present and no mucus. The food left the stomach rather quicker than was normal.

At this time a diagnosis of achylia gastrica was made and the patient advised to have his abscessed teeth cared for. He lived out of the city and said this would be done. Patient was not seen again for a period of four years. He returned for examination in November, 1919. At this time the predominating complaint and trouble was referred to the blood. The clinical picture was that of a pernicious anemia. The hemoglobin was 48 per cent, red blood cell count 2,120,000, color index 1.1, the white count 4,850. Differential blood count was as follows: Polymorphonuclear 82 per cent, small lymphocytes 12 per cent, large mononuclears 5 per cent, eosinophiles 1 per cent, mast cells 0.

The stained specimen showed distinct evidences of polychromasia, anisocytosis, and poikilocytosis. The clinical picture was very definitely characteristic. The color of the skin was pale, sallow, and slightly yellow. There were sensory disturbances of both legs, feeling of prickling and numbness on the soles of the feet and calves of the legs. However, the reflexes were all retained in their normal way. Examination of the stomach contents at this time showed a persistence of the achylia gastrica with findings very similar to those of four years before. The condition of the teeth showed a large number of alveolar abscesses as revealed by the x-ray and tonsils definitely infected. The tongue was very red and there was a complaint of soreness or pain from occasional attacks of stomatitis.

The origin of pernicious anemia is not yet solved. However, many clinicians have definite opinions that such anemias have a connection or relationship with persisting infections wherever they may be localized. The fact that examination may not reveal such infections in particular instances is not a satisfactory reason for excluding them, in view of the great difficulty of determining obscure infectious processes in such inaccessible places as some of the deeper bony sinuses, the bile ducts, intestinal canal, pelvic organs, and other structures.

The work already done has convinced most clinicians that local infections, especially of the more pronounced types, can produce functional disturbances in practically any organ of the body. It is reasonable to assume that such long continued infections may produce an achylia gastrica with a persistently low gastric secretion such as was present in the three cases here cited. The presence of achylia gastrica in a patient showing a severe chronic focal infection should put one on his guard against a possible oncoming per-

nicious anemia developing. It cannot be said that even the removal of all foci during the pre-anemic stage would prevent the development of a genuine pernicious anemia but it may be urged that the removal of such foci is highly desirable in the hope of preventing such a development. The association of achylia gastrica and pernicious anemia is so well known that these cases are cited only with the intent of calling attention to the sequence of focal infection—achylia gastrica—anemia in this respective order. If this chain can be broken even occasionally it means a human life saved, which is sufficient reason for the citations herein mentioned.

CONCLUSIONS

(1) Three cases are cited, in each of which patients having foci of severe infections passed through the stage of an achylia gastrica and later pernicious anemia.

(2) The assumption that long continued foci of infection may depress the gastric secretion and produce an achylia gastrica is justifiable.

(3) There is no reason to believe, on the basis of any evidence yet brought to bear, that achylia gastrica in itself is a predisposing cause of pernicious anemia.

(4) There is clinical evidence to believe that focal infections long continued may depress the function of the bone marrow and prevent the formation and development of new red blood cells.

(5) It is urged that when achylia gastrica is discovered in a patient showing evidences of chronic focal infections that the possibility of the development of pernicious anemia be carried in mind with the view of insisting that all infections be removed insofar as is humanly possible. Achylia gastrica is used here in the sense of a depression of the gastric secretion with relation to HCl and not necessarily with complete absence of gastric ferments.

II. THE VALUE OF THE REFRACTO-VISCOSIMETRIC PROPERTIES OF THE BLOOD SERUM IN CANCER*

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IN a previous paper studies recorded on the blood of syphilitic patients showed that there is a definite decrease in the refracto-viscosimetric quotient which is attributed to an increase in the serum-globulin. It was further demonstrated that treatment for syphilis had a marked influence on this quotient, with a tendency to bring it to normal.

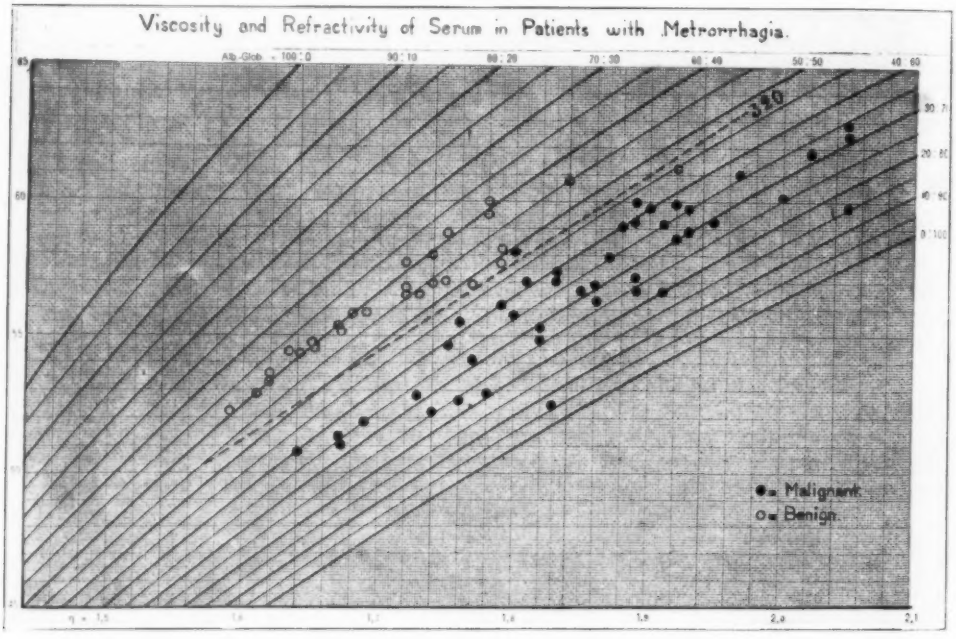

Fig. 1.

The examination of patients in the Mayo Clinic revealed a decreased quotient in various other diseases, such as cancer, tuberculosis, actinomycosis, and sarcoma. The findings in relation to cancer were selected for the present study.

The knowledge on this subject seems to be restricted, and though my study is in some ways a duplication of Loebner's work, it may be of value in confirming and correcting some of her findings. A discussion of some of the points in Loebner's conclusions will readily reveal the new aspect of the problem. Loebner calculated the amount of protein in the serum with the aid of

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the refractometric index and the table of Reiss. I have not made this calculation as there are still some questionable points in the procedure. I have, however, confirmed Loebner's statement, that there is usually no decrease in the concentration of the serum of cancerous patients. The color of the serum in Loebner's cases was normal in twenty-one instances, darker than normal in twelve, and lighter in ten. In my series all possible shades from dark golden to light yellow were observed, which seems to indicate that the color is not of particular significance. Another point is of unusual interest. The refractivity and the viscosity of the serum were used in connection with the chart of Naegeli[2] to determine the albumin-globulin ratio. The most important conclusions are, that globulin is usually increased, that an improvement may be accompanied by a decrease in globulin and an unfavorable course by an increase. These conditions, however, were not absolutely constant.

TABLE I

SERUM OF ONE HEALTHY PERSON EXAMINED OVER A PERIOD OF SIX MONTHS

TEST	EXPERIMENT	DATE	REFRACTIVITY	VISCOSITY	REFRACTO-VISCOSIMETRIC QUOTIENT	ALBUMIN	GLOBULIN
1	383	6/26	53.4	1.62	330	60	40
2	399	6/28	53.6	1.62	331	61	39
3	401	6/29	54.5	1.65	330	60	40
4	404	6/30	54.5	1.63	334	63	37
5	421	7/ 9	53.6	1.62	331	61	39
6	434	7/13	54.3	1.65	329	59	41
7	445	7/15	55.3	1.67	331	60	40
8	451	11/ 2	52.9	1.61	329	60	40
9	460	11/ 5	55.8	1.68	332	60	40
10	468	11/ 7	54.7	1.65	331	60	40
11	473	11/16	53.6	1.62	331	61	39
12	478	11/18	54.3	1.64	331	60	40
13	488	11/22	53.8	1.63	330	60	40
14	500	11/29	54.9	1.64	335	63	37

TABLE II

SERUM OF WOMEN WHO HAD SYMPTOMS OF SEVERE METRORRHAGIA CAUSED BY BENIGN PELVIC TUMORS

TEST	EXPERIMENT	PATIENT	REFRACTIVITY	VISCOSITY	REFRACTO-VISCOSIMETRIC QUOTIENT	ALBUMIN	GLOBULIN
1	418	363948	58.0	1.74	333	59	41
2	374	361033	60.8	1.84	330	55	45
3	419	363537	56.9	1.74	327	54	46
4	446	375874	57.6	1.79	322	48	52
5	447	361040	55.8	1.69	330	58	42
6	450	163113	58.8	1.75	336	61	39
7	457	5256	61.1	1.92	318	44	56
8	458	243767	56.9	1.77	322	49	51
9	461	376368	58.2	1.79	326	51	49
10	465	376220	56.5	1.73	327	54	46
11	467	347728	56.9	1.75	325	52	48
12	470	363504	57.6	1.72	335	61	39
13	474	145680	55.3	1.67	331	60	40
14	475	377472	60.0	1.78	337	62	38
15	476	377138	56.7	1.73	328	57	43

The results given in Tables I to IV are evidence that globulin is increased in the serum of patients affected by a cancerous growth. This increase was found much more constantly than in Loebner's cases. Because of my previous criticism[2] it seemed advisable to compare the refractive and the viscosimetric findings without using the chart of Naegeli. Both of these physical properties depend largely on the protein content. A variation in the ratio of refractivity and viscosity is probably due to a change in the constituents of the protein or the serum as a whole. I cannot prove at this time the possibility that the variation depends entirely on the albumin-globulin ratio, and such an assumption is not even necessary with our present knowledge.

The refractive and the viscosimetric index of serum can be determined with great accuracy.[2] The quotient of refractivity and viscosity which has never been calculated in the form presented here, can be obtained as follows: For convenience the refractive index is expressed in Pulfrich's units.[2] These are multiplied by ten and divided by the viscosimetric index.

Example: $\frac{56.0 \times 10}{1.75} = 320.$

TABLE III

WOMEN WHO HAD SYMPTOMS OF METRORRHAGIA CAUSED BY CANCEROUS GROWTHS OF THE PELVIC ORGANS

TEST	EXPERIMENT	PATIENT	REFRACTIVITY	VISCOSITY	REFRACTO-VISCOSIMETRIC QUOTIENT	ALBUMIN	GLOBULIN
1	336	358916	58.0	1.87	310	36	64
2	340	358747	59.7	2.05	291	15	85
3	343	310843	59.3	1.95	304	29	71
4	353	349567	61.1	1.97	310	36	64
5	356	360742	62.5	2.05	305	32	68
6	407	334314	59.7	1.93	309	35	65
7	417	363839	55.6	1.76	316	43	57
8	420	361822	54.1	1.77	306	31	69
9	423	363880	53.8	1.73	311	38	62
10	428	361545	55.8	1.80	310	36	64
11	436	364539	56.9	1.86	306	31	69
12	438	362571	52.7	1.76	299	25	75
13	439	344862	54.9	1.82	301	26	74
14	442	363405	52.9	1.78	297	21	79
15	448	196042	60.0	1.89	317	43	57
16	449	375704	56.2	1.79	314	40	60
17	452	375314	61.8	2.02	306	32	68
18	453	374060	58.7	1.92	306	31	69
19	454	374790	56.7	1.85	306	32	68
20	455	376119	57.1	1.83	312	38	62
21	456	312183	57.1	1.89	302	26	74
22	459	139903	51.3	1.67	307	36	64
23	464	375722	60.0	1.94	309	35	65
24	466	375928	56.5	1.86	302	29	71
25	469	376627	51.8	1.69	306	35	65
26	471	376800	56.7	1.91	297	20	80
27	473	376005	58.2	1.80	323	49	51
28	477	377432	57.6	1.81	319	45	55
29	483	370087	60.4	2.08	290	15	85

DISCUSSION

In Table I a basis is given for the study of physiologic and instrumental variations. The fact that changes in refractivity and viscosity are parallel to such an extent that the quotient is almost constant, eliminates great instrumental errors. Such errors would not affect both readings in the same sense. Under physiologic conditions the variation of the refractivity and of the viscosity is very slight. The refractivity varied from 52.9 to 55.3, and the viscosity from 1.61 to 1.67 with an average of 1.64. The average refracto-viscosimetric quotient is 331. The ratio of albumin to globulin as determined by Naegeli's chart shows an average value of from 60 to 40 and is within physiologic limits. This ratio cannot claim absolute validity because it is based on an indirect determination.

TABLE IV

SERUM OF PATIENTS SUFFERING FROM VARIOUS FORMS OF CANCER

TEST	EXPERIMENT	PATIENT	LOCATION	REFRACTIVITY	VISCOSITY	REFRACTO-VISCOSIMETRIC QUOTIENT	ALBUMIN	GLOBULIN
1	331	358074	Abdomen	62.7	2.05	306	32	68
2	332	380465	Tongue	59.7	1.90	314	40	60
3	333	337562	Parotid gland	59.3	1.89	314	40	60
4	335	336595	Lip	54.7	1.75	312	40	60
5	367	356499	Lip	60.2	2.01	299	25	75
6	368	358192	Breast	59.3	1.91	310	36	64
7	369	358184	Rectum	52.4	1.83	287	6	94
8	393	360922	Stomach	52.2	1.74	300	25	75
9	405	322725	Rectum	50.8	1.64	310	40	60
10	406	362672	Parotid gland	58.9	1.93	305	30	70
11	410	362897	Penis	55.3	1.82	304	29	71
12	411	362475	Breast	57.1	1.81	316	42	58
13	415	362246	Stomach	51.1	1.67	306	35	65
14	416	362077	Breast	56.7	1.89	300	25	75
15	429	310127	Breast	57.3	1.83	313	40	60
16	440	329726	Bladder	59.1	1.88	314	40	60
17	329	359511	Vulva	57.1	1.85	309	35	65
18	375	–	Breast	56.9	1.81	315	40	60
19	431	331309	Breast	58.5	1.84	317	44	56
20	479	376037	Breast	58.2	1.85	315	40	60
21	480	377351	Breast	56.2	1.76	319	46	54
22	482	377938	Vagina	55.3	1.78	311	37	63
23	484	376159	Rectum	54.7	1.78	307	33	67
24	485	375819	Rectum	54.9	1.79	307	32	68
25	486	371442	Rectum	54.1	1.90	285	4	96

Table II demonstrates the fact that the blood of women with benign tumors is not affected. Refractivity and viscosity are within normal limits with one or two exceptions. The refracto-viscosimetric quotient ranges from 318 to 337, with an average of 328. The percentage of globulin is generally below 50 and rises slightly above it in three cases. It may be considered as normal.

Table III forms a certain contrast to Table II. All of the cases are malignant. The refractivity remains normal, while the viscosity of the serum is, as a rule, increased. Consequently the refractoviscosimetric quotient is de-

creased. The average is 307. The globulin percentage is decidedly increased, the average lies between 60 and 70.

In Table IV the findings of uterine cancer are generalized, showing that malignancy in any organ affects the refractoviscosimetric quotient in the same sense. It is markedly decreased.

CONCLUSION

The first series of experiments proves the validity of the technic and demonstrates the great constancy of the refractoviscosimetric quotient under normal conditions. The pathologic material gives evidence of marked change in the physical findings in the serum. While benign tumors do not affect the blood, any form of cancer causes a definite alteration. This can best be expressed by the refractoviscosimetric quotient which, in normal conditions, is almost always above 320, and in malignancy below 320, as shown in the chart.

ADDITIONAL POINTS IN THE TECHNIC OF THE DETERMINATION OF REFRACTIVITY AND VISCOSITY

1. In every paper dealing with the refractivity and viscosity of serum it has been emphasized that congestion of the vein before taking the blood sample modifies the result. In this study venous blood, obtained through a large needle, was used. The compression usually lasted only a few seconds, the blood flowed freely, and the first cubic centimeter was not taken. In order to determine whether or not congestion has a bad effect, blood was first withdrawn in the usual manner; a second sample was drawn after one minute, a third after two minutes, and a fourth after three minutes of intensive compression of the vein. The refractivity and the viscosity remained practically the same.

2. Samples of serum kept in the ice box for eight hours showed the same viscosity as those kept at room temperature.

3. The viscosity of the serum did not change if the serum was left with the blood clot for eight hours.

4. Serum obtained by centrifuging the sample of fresh blood showed the same viscosity as serum collected after the spontaneous retraction of the blood clot.

5. From a number of persons two blood samples were taken, in one of which slight hemolysis was produced. It was found that slight hemolysis does not alter the viscosity of the serum.

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LABORATORY METHODS

SUGGESTED ADAPTATION TO THE GASOMETER METHOD OF THE DETERMINATION OF THE BASAL METABOLIC RATE FROM CARBON-DIOXIDE ELIMINATION*

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DETERMINATION of the basal metabolism has become a common procedure and many methods of indirect calorimetry have been developed. In the Tissot gasometer method, described fully by Boothby and Sandiford,[1] the patient inhales fresh air, the exhaled air being analyzed for O_2 and CO_2 content. The closed system described by Benedict[2] affords estimation of O_2 absorbed by volume, and CO_2 produced by weight. Other closed methods which are in most common use today deal with the O_2 consumption alone, assuming a respiratory quotient of .82 as described by Jones,[3] and by Benedict and Collins.[4]

In the routine use of the Tissot method with analysis of air by means of the Haldane apparatus, certain technical difficulties are found. These, however, are not in the collection of the exhaled air in the gasometer, which with properly working valves in the air conducting system gives satisfactory results. It is the air analysis, particularly the determination of the oxygen content, that involves the greatest technical difficulty. The estimation of the CO_2 content of a sample of exhaled air yields quite constant and accurate percentages which are easily checked. The estimation of O_2 by absorption in pyrogallic acid is a considerably longer process. The variability in rate of absorption with the increased time necessary makes the process more subject to error. Experience with new technicians convinces one that to obtain accurate O_2 estimation by this method requires several months' training.

For some months it has been noted that approximation of the basal metabolic rate could be obtained by finding the CO_2 content of the exhaled air and using an average total CO_2 plus O_2 content. A series of 18 cases is found in Table I in which the average results obtained when a constant figure was used for total CO_2 plus O_2 with estimation of CO_2 only, are compared with the results obtained when the individual values of O_2 as well as CO_2 were determined. The variation in the results obtained is in no individual case greater than 7 per cent and in 18 cases the average difference is 3.5 per cent. Such variation was not sufficient to alter the clinical interpretation of the values obtained in any case.

Recently King[5] has studied protocols of two groups of experiments with the Atwater Chamber Calorimeter by Benedict and Carpenter, and by Sonder-

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TABLE I

Comparison of values obtained for the basal metabolic rate
(a) when the amounts of O_2 and CO_2 produced are obtained for each patient,
(b) when the CO_2 produced only is obtained and an average total CO_2 plus O_2 figure is used.

CASE NUMBER	(A)	(B)	CASE NUMBER	(A)	(B)
1	+34	+29	10	+19	+16
2	+27	+25	11	+ 2	- 3
3	-12	-13	12	+ 4	- 2
4	- 2	- 5	13	+93	+97
5	+24	+27	14	+ 2	- 5
6	+59	+54	15	+ 4	- 2
7	+ 1	0	16	+17	+12
8	- 4	- 7	17	0	+ 1
9	-15	-16	18	+10	+ 4

strom, Meyer and Du Bois and has shown from their figures that there is a somewhat higher coefficient of correlation between CO_2 and measured calories than between O_2 and measured calories. He describes a method of determining the basal metabolic rate from the CO_2 content of exhaled air, using the open method with collection of the CO_2 in soda lime and estimation of its weight, and proposes a scale of normal figures* representing grams of CO_2 produced per hour per square meter of body surface, for men and women of different ages. King obtained this scale from his own findings in seventeen normal individuals averaged with the findings of Benedict, Emmes, Roth and Smith. King concludes that the CO_2 elimination seems to be at least as accurate and possibly a more accurate index of heat production than the O_2 consumption. In 1862 Pettenkofer[6] had constructed a respiration apparatus in which only the amount of CO_2 produced was measured and Voit calculated the heat production in the body using heat values obtained in his laboratory for protein, fat and carbohydrate.

Besides the indirect approximation of the basal metabolism which, for a considerable time past, we have observed to be possible, as evidenced by the series of cases in Table I, the direct estimation of CO_2 elimination with comparison to normal figures lends itself readily to the Tissot method and volumetric determination of the CO_2 content. The advantages of the open method are evident, with its prevention of the danger of respiratory infection and the lessened disturbance to the patient with the open mask. The technical difficulty of determining CO_2 volumetrically is scarcely, if any, greater than its determination by weight, and while correction must be made for temperature and barometric pressure, the use of scales is obviated.

To those who have the Tissot spirometer and do not have an expert air analyst, the estimation of CO_2 volumetrically would seem to give more accurate information than O_2 consumption figures obtained by other than thoroughly

*CO_2 production in grams proposed by King for normal individuals.

Ages	Men	Women
15-20	14.03	12.75
20-30	12.98	11.95
30-40	12.86	11.85
40-50	12.52	11.74
50-60	12.21	11.37
60-70	11.86	11.05
70-80	11.53	10.71

experienced technicians; CO_2 absorbs quite rapidly in the sodium-hydroxide solution and check readings are readily obtained. The apparatus necessary is simplified when the CO_2 content only is determined since that portion of the Haldane apparatus used in the absorption of O_2 in pyrogallic acid can be done away with. Besides simplification of apparatus there is shortening of computation.

The volumetric method has the added advantage of giving the total ventilation of the lungs for a certain definite period of time, which is not obtainable with the weight method of determining CO_2. A series of twenty-six cases is given in which the basal metabolic rate obtained from complete air analysis is compared with that obtained from CO_2 produced. The variation in no case is greater than 6 and averages about 3 per cent. Results obtained check well with clinical diagnosis. The computation simply consists of taking the total ventilation, per hour, corrected to standard temperature and barometric pressure × per cent CO_2 × 1.96 (to convert liters CO_2 to grams) ÷ surface area (Dubois formula) with comparison to proposed normal figures for CO_2 elimination.

In another series of thirty-three routine determinations with complete air analysis computations were made by assuming an average respiratory quotient of .82. The oxygen was then estimated by the simple ratio, $\frac{CO_2 \text{ produced}}{\times \text{ (oxygen absorbed)}}$

TABLE II

Table II shows comparative values for the basal metabolic rate when obtained from the CO_2 eliminated and when obtained by the estimation of both O_2 absorbed and CO_2 produced.

	NAME	AGE	BODY SURFACE DUBOIS FORMULA	CO_2 ELIMINATED PER HR. PER SQ. M. BODY SURFACE (GMS.)	PER CENT DEVIATION OF CO_2 PRODUCED FROM AVERAGE	THE BASAL METABOLISM PERCENTILE, USUAL O_2 ABSORPTION AND CO_2 ELIMINATION ESTIMATION
1	S.E.B	24	1.5	13.96	+16	+13
2	M.R.B.	29	1.56	17.53	+35	+30
3	H.O.B.	28	1.66	13.01	+ 8	+8
4	N.E.B.	52	1.43	11.40	+ 0.2	− 1
5	J.A.B.	27	1.73	18.08	+39	+40
6	J.A.B.	27	1.76	11.71	−10	−9
7	S.E.B.	24	1.5	13.41	+12	+ 9
8	H.O.B.	28	1.66	13.33	+11	+ 9
9	A.N.B.	46	1.71	11.80	+ 0.5	0
10	E.D.B.	16	2.34	12.18	− 4	−10
11	A.U.B.	30	2.00	11.75	− 9	−11
12	L.A.B.	23	1.62	12.51	+ 4	0
13	S.B.	23	1.72	12.90	+ 4	+2
14	S.B.	23	1.73	10.48	−12	−15
15	C.B.	37	2.2	11.78	− 0.5	− 2
16	M.W.	28	1.345	15.51	+29	+27
17	W.H.A.	33	1.87	11.51	−10	−12
18	R.A.A.	29	1.84	12.77	− 2	− 2
19	A.A.	26	1.51	18.88	+58	+59
20	N.A.	31	1.63	10.88	− 8	− 8
21	G.A.	42	2.08	10.79	− 8	−10
22	M.A.	29	1.68	13.27	+ 2	+ 1
23	M.A.	52	1.76	11.05	−9	− 8
24	H.B.A.	48	1.615	13.39	+14	+10
25	V.A.	24	1.52	13.76	+15	+17
26	L.A.	23	1.86	13.88	+ 6	0

= .82, the CO_2 value only being actually determined. The values thus obtained were compared to those from complete air analysis in the same cases and to those from CO_2 production in grams. The average variation from complete air analysis in the computed basal metabolism was 4.8 per cent, from CO_2 production in grams 3.4 per cent. A maximum variation in a diabetic with a respiratory quotient of .70 was 14 per cent in the former instance and 12 per cent in the latter. It is apparent that estimation of the basal metabolism from CO_2 production is not applicable in pathological conditions in which the respiratory quotient is greatly altered. In the series studied, computation with an assumed respiratory quotient gave only a slightly greater variation than the CO_2 production in grams from the basal metabolism values of complete air analysis.

In diabetes with its altered respiratory quotient and in acidosis, CO_2 elimination has a limited value only. Certain cases of obesity have also shown an altered respiratory quotient and in this condition estimation of CO_2 elimination may be of limited value. CO_2 produced can be readily determined volumetrically with usual care and, in small clinics and laboratories where an experienced air analyst is not available, may be used as a relatively accurate index to the basal metabolism.

CONCLUSIONS

1. Adaptation of the CO_2 determination of the basal metabolism to the Tissot spirometer is suggested.

2. This method has the advantage of all open methods, with less danger of infection and less disturbance to the patient.

3. The total pulmonary ventilation is obtained with the volumetric determination of the CO_2 which is not possible with the weight method. The method is simple and results can be readily checked.

4. Results obtained by this method in a series of 26 cases give satisfactory clinical evidence and check well with those obtained by complete air analysis. In another series of thirty-three routine determinations comparison of results from CO_2 production in grams to complete air analysis showed a maximum variation of 12 per cent in a diabetic with a low respiratory quotient. In that condition satisfactory checks with complete air analysis were not obtained.

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THE CLINICAL VALUE OF BASAL METABOLISM DETERMINATION*

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THIS paper briefly reviews the literature on the diagnostic value of the test, reports illustrative cases, with notes on the method of the test.

Of the calories kinetic in the food each day the part expended dynamically in work varies with the individual and with the task, but the part that is expended in keeping the vital processes going, that keeps the vital machine running, has been found not variable in the individual, and in different individuals has been found so closely proportional to height, weight, sex, and age that the normal can be predicted with negligible error. This necessary minimum of activity is the basal metabolism. Studies in diseased conditions, exclusive of fevers all of which give an increased rate, have shown the most definite groups with abnormal basal metabolism to be those cases with disturbances in the activity of the thyroid gland. McCaskey says "while recognizing the paramount position of the general clinical judgment in every case, variations in the basal metabolic rate as indirectly determined by oxygen consumption must be regarded as the most scientific and practical index of thyroid 'toxicity.'"[1] Boothby states that at least 95 per cent of all abnormally increased rates are due to hyperthyroidism if there is no fever.[2]

Increased basal metabolic rates are found in hyperthyroidism, in all febrile conditions, and in the active state of acromegaly[3]. In other diseases as essential hypertension, pernicious anemia, leukemia, diabetics with acidosis, cases with dyspnea, a rate above normal may be present occasionally. A decreased basal metabolism is always present in myxedema, in cretins, and in a lesser degree in hypopituitarism; the rate is low in inanition, starvation, and undernourished diabetics. Excluding these few other conditions changes in the basal metabolic rate are due to thyroid disease. The determination of basal metabolism in thyroid disease is like the use of the thermometer in febrile diseases and answers the same purpose of diagnosis, measuring the severity, marking the course of the disease and the effect of treatment.

A routine estimation of the basal metabolism should be made (1) in cases with goiter to ascertain possible toxicity; (2) in cases with or without goiter having symptoms resembling those caused by hyperthyroidism; (3) in similar cases with symptoms of thyroid deficiency; (4) in cases of obesity to differentiate those due to thyroid and pituitary disease[4]; (5) for an accurate measure of the effect of treatment of thyroid disease.

The diagnostic value of the basal rate is greatest in the group of cases with one or more of the symptoms of those caused by hyperthyroidism. Cardiac disturbances as tachycardia, cardiac myasthenia, and palpitation; fine

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tremors, general debility, loss of weight, anemia, attacks of vomiting and diarrhea, psychic changes as depression and irritability, psychasthenia, sweats, are symptoms obviously of the most diverse etiology, but are symptoms which the exclusion of thyroid disturbance or its acceptance as cause can be made by a determination of the basal metabolism "as the final court of appeal."[5] This test is especially useful in the differential diagnosis of hysteria, neurasthenia, early tuberculosis, and neuroses simulating thyroid disease. It is necessary in the diagnosis of "effort syndrome," Da Costa's irritable heart of soldiers, in which there is an increased sensitiveness to epinephrin but a normal basal rate. There has been needless confusion due to the exploitation of the epinephrin reaction. Epinephrin raises the basal metabolism but no relation has been found between the amount of the rise and the intensity of a hyperthyroidism, its effect being attributed to action on the sympathetic nervous system; "there is no evidence that the group of neurasthenics with a positive epinephrin reaction and a normal basal metabolism is dependent on variations in the secretion of the thyroid gland."[6] Likewise effort syndrome may be confused with the hyperthyroidism caused or brought out by the strain of service life in young men, in whom the thyroid enlargement of adolescence is not uncommon. The value of basal metabolism estimation in conditions at the time of the change of life in men as well as in women, when glandular balances are upset, is a field for interesting work. The rôle of the thyroid at this time of life is suggested by the inclusion of thyroid extract in the polyglandular treatment empirically used with clinical success. Metabolic work alone can determine the actual part of the thyroid in the phenomena of senescence.

DuBois in his paper on exophthalmic goiter says: "Exophthalmic goiter stands out as the disease of increased metabolism, and the increased metabolism stands out as the chief symptom of hyperthyroidism. The determination of heat production seems to afford the best index of the course and severity of the disease. There was great need for some purely objective test in hyperthyroidism to indicate the effect of treatment."[7] Many of the other symptoms are simply the effect of the increased heat production, all are variable and difficult to measure. "The rapidity of the heart action is perhaps the best guide, but the heart is often affected by other conditions, and damage to the heart may outlast the other symptoms. The sugar tolerance test depends on other glands as well as the thyroid, and has wide limits even in health." "In contrast to the other symptoms an increased basal metabolism is found with great regularity in exophthalmic goiter and in severe cases reaches a level found in no other condition. On the other hand in cretinism and myxedema the metabolism is lower than in any other disease. The administration of thyroid extract particularly in myxedema, raises the heat production." As Plummer states, "the thyroid produces its effect through metabolic processes."[8]

The basal metabolic rate gives a precise measure for the selection of treatment and the determination of its effect if any in diseases of the thyroid. It affords a mathematical measure of comparison between different cases for systematic study. Means and Aub[9] state that the level of the basal metabolism

TABLE I

CASES FOR DIAGNOSIS

CASE	SEX	AGE	HT. CM.	WT. KG.	OX. VOL. P. 10M.	CAL. P. DAY	NOR. CAL. BM PER D.	% VAR.	DIAGNOSIS FROM TOXIC THYROID
1	M	23	180	66.8	2311	1618	1730	7–	Goiter, tremor, p. 60, sweats, "nervous," nontoxic adenoma plus neurosis
2	M	22	166	55.1	4647	1622	1506	8+	Neurosis, myocarditis, local tetany
3	M	21	171	49.6	1935	1355	1463	8–	Intention tremor, multiple sclerosis
4	F	39	166	58.3	1881	1295	1338	3–	Tachycardia, tremor; cardiac
5	M	31	180	78.6	2768	1938	1838	5+	Irritable heart
6	F	27	155	46.	1917	1342	1255	7+	Neurosis following several operations
7	M	23	184	74.5	2764	1958	1856	5–	P. 70, tachycardia on exercise, tremor, irritable heart.
8	F	29	163	53.5	1839	1288	1333	4–	Goiter, loss weight, "nervous," nontoxic
9	M	23	175	58.	2201	1517	1584	4+	P. 100, loss weight, nervous, valv. heart dis.
10	M	38	177	72.4	2579	1805	1691	6+	Asthenia, alpit., impotence, psychasthenia
11	M	20	182	70.3	2608	1826	1910	4–	Goiter, tachycardia; cardiac
12	M	25	172	57.4	2267	1588	1548	2+	Mitral regurg., neurosis; prev. diag. thyrotoxicosis
									DIAGNOSIS THYROTOXICOSES
13	M	20	187	74.6	3360	2352	1893	24+	P. 114, pulse press. 70, early ex. goit.
14	F	25	176	51.1	2176	1524	1353	13+	P. 96, goiter, hot sens., loss weight, dilat. heart, hyperthyroidism
15	M	26	172	50.5	2387	1671	1446	15+	Small goiter, tremor; hyperthy. and tbc.
16	M	26	174	60.1	2510	1758	1588	11+	Goit., trem., loss wt., mild toxic goit., quinin. hbr., 3 mo., BM 3+, no symp. well
17	M	27	171	67.4	3317	2322	1666	39+	P. 98, trem., palp., no g., no ex.; toxic thy.
18	F	41	165	46.1	1965	1376	1209	14+	P. 88, palp., goit., nervous; mild toxic
19	M	20	173	76.5	3118	2183	1849	18+	P. 87, goiter, tremor; mild toxic
20	M	28	180	61.4	2666	1867	1619	15+	P. 70, goit., tachy.; hyperthy. and mitral
21	M	20	178	68.2	2976	2084	1760	18+	P. 75, goit., trem., palpit.; mild toxic
22	M	21	176	61.	2895	2027	1623	25+	P. 75, trem., tachy., nervous, hyperthyr.
23	F	33	157	56.4	3603	2496	1330	88+	P. 120, no goit., no exoph.; tremor, diarrhea

Height in centimeters, weight without clothes in kilos, corrected volume of oxygen retained per 10 minutes, calories basal rate per day (observed), and normal prediction per 24 hours, basal metabolism, from Harris-Benedict tables.

is a better guide to the degree of thyroid lack in hypothyroidism than the clinical picture and that the proper dosage of thyroid is best measured by the effect on the metabolic rate. (They found an average of 3 to 4 grains per day of thyroid extract brought the rate to normal, and 1 or 2 grains would keep it there.)

In hyperthyroidism the operative risk should be gauged by this test judged in combination with the other symptoms, particularly the cardiac reserve, and the need or character of surgical or medical treatment considered on an objective basis as much as possible. Rates of 100 plus or over are dangerous, and should be reduced by absolute rest in bed. Rates of 75 plus, very severe, rest, hot water injections or ligations, should be considered preliminary to partial thyroidectomy. Lahey and Jordan[10] warn against primary thyroidectomy in most cases with a rate of over 35 plus. This is very conservative. There are a few atypical cases of hyperthyroidism with rates almost normal. Sandiford[3] had 22 patients with an average basal rate of 66 plus, pulse 123; after two ligations and rest in bed the rates averaged 46 plus, pulse 115. Three months later the rates averaged 39 plus, pulse 107, and at discharge after thyroidectomy the rates averaged 16 plus, pulse 89. The three month interval between ligation and partial thyroidectomy seems to be too long. The basal rate should be tested every two weeks, and the operation timed accordingly. Of the cases cited 14 had a rate at the time of operation as high as before or higher. In exophthalmic goiter a second or third partial thyroidectomy may be indicated, or the x-ray may be used to bring metabolism to normal.

The Roentgen ray treatment has been compared with surgical results by Means and Aub.[11] "In the third year x-ray and surgery were alike," all patients were leading normal lives, rates averaged 13 plus, for both, the x-ray gave equally good results and in cases of equal toxicity there was less danger. They suggest using x-rays first, a cure may be effected, at least the metabolic rate will be reduced and surgery made safer. If the basal rate is high after surgery the x-ray may be employed again. Means' latest report is still more favorable to the x-ray in that the patients treated by the rays were normally active during the course of treatment.[12] Occasionally a case will not react favorably to the rays. Some surgeons object to the increased difficulty of the operation from fibrosis. DuBois says a partial thyroidectomy has been and perhaps always will be standard treatment.

The cases selected for Table I were referred for diagnosis, based on the metabolic rate.

Both groups in Table I had about the same clinical appearance, with palpitation, tremors, goiter, "nervousness"; the diagnosis was made on the basal metabolism, one group of cases largely cardiac, the other thyrotoxicoses. The male patients in both groups were service men in the Navy and from the War Risk Insurance Office, referred by Drs. Reed, Derbyshire and McDowell. Case 14 referred by Dr. Churchill, and 16, from Dr. Reed, are examples of possessing a low basal rate, scarcely above normal (13+ and 11+) with mild toxic symptoms; 23, referred by Dr. Churchill, without goiter or exophthalmos, had a basal rate of 88 plus, tremor, diarrhea, a severely toxic case.

TABLE II

CASES SHOWING EFFECT OF REST

CASE	SEX	AGE	HT. CM.	WT. KG.	OX. VOL. P. 10M.	CAL. P. DAY	NOR. CAL. BM PER D.	% VAR.	
1	F	35	166	44.1	2985	2076	1197	73+	Dec. 3, 1920, p. 132, severe exoph. goiter
				46.8	2229	1560	1224	27+	March 22, 1921, p. 96, absolute rest in bed
2	M	30	178	57.4	2981	2087	1551	35+	Oct. 23, 1920, p. 70, thyrotoxicosis
				57	2710	1898	1545	23+	Dec. 31, rest on ranch
				58.7	2604	1823	1569	16+	March 3, 1921, on ranch, light work, improved
3	M	44	176	56.5	2488	1742	1551	14+	June 21, seven x-ray treatments since March
				48.6	2339	2362	1552	74+	Oct. 6, 1920, p. 108, exoph. goiter
				53.8	3081	2157	1389	55+	Oct. 12, ⅔ gland removed, Dr. McDowell
				58.1	3408	2386	1498	65+	Dec. 24, p. 100 irreg., very nervous
				57.	3629	2541	1433	77+	March 7, 1921, p. 100 irreg., very toxic
			Still classic ex. goiter, severe myocarditis, inoperable						June 24, p. 100 irreg., getting x-ray treatment
4	M	24	188	76.9	4131	2892	1903	52+	April 28, toxic adenoma
				76.8	3430	2402	1902	26+	June 23, rest only
5	F	33	156	52.2	1797	1258	1288	3–	Tremor, palpitation, p. 118, Two months
			Previous BM 15+, quieted by rest only.						Op. Dr. C. M. Fox, toxic adenoma.

Case 3 Table II in spite of a 4/5 thyroidectomy had a return of the full toxicity and with this a damage to the myocardium that makes the outlook discouraging. Rest was without effect, in his case, at present he is getting x-ray treatments. Rest in the last two cases brought the basal rate down to where the operative risk is minimal. Case 2 reached the limit of improvement for him with rest at 16 plus, but symptoms were more severe than the rate indicates. The roentgen treatments are causing a steady return to normal.

Case 1, Table III, was brought from 35 plus to 10 plus by rest alone with corresponding amelioration of the hyperthyroidism as regards other symptoms. A month later the rate was 25 plus, weekly x-ray treatments improved symptoms and reduced the rate. Case 2 referred by Dr. L. C. Kinney, had hyperthyroidism and a functional heart disturbance, he treated the patient with x-rays resulting in a symptomatic cure, rate 1 minus, the patient returned to college. Case 3 also given roentgen treatments by Dr. Kinney shows a gradual improvement under adverse circumstances. He had had a partial thyroidectomy in 1918, but in Oct., 1920, had a return of his goiter, a severe exophthalmic, and was studying in a business college. Dr. Kinney increased the dose of rays in Feb., 1921, when the basal rate had gone up to 30 plus again, and by July the patient was well except for the exophthalmos. Case 5 neglected to report for the metabolic test and the actuality of the effect of the rays on the thyroid was demonstrated in a rate of 36 minus, patient weak, she could hardly get about. Treatment was discontinued and the thyroid returned to normal, patient well. Case 6 referred by Dr. Fox had symptoms rather more toxic than the rate of 10 plus, accepted as the normal limit, indicated. X-ray treatments reduced the rate, relieved the nervousness and tachycardia, and as shown there was a gain of 3.7 kg. Case 7 was referred to Dr. Kinney for x-rays as hyperthyroidism. The basal rate in spite of hyperthyroid symptoms, was 19 minus. Thyroid extract increased the toxicity, so on the diagnosis of dysthyroidism Dr. Kinney gave irritating doses of the roentgen ray, with symptomatic cure, normal basal rate, and gain in weight.

Operative results followed have shown about the same results as reported by others; a complete cure in the case of toxic adenomas, and often discouraging immediate results in the exophthalmic goiters. Case LH, rate 63 plus, pulse 130-160 was practically unaffected by x-rays. Operation by Drs. Oatman and Rees, 2/3 thyroidectomy, brought the rate to 15 plus, pulse 80, she had had a severe exophthalmic goiter. Other cases have had recurrence. There are some cases that are almost uninfluenced by any method of handling. Three toxic adenomas, with rates of 13 plus, 45 plus, and 41 plus, operated on by Drs. McDowell, Fox, and Oatman respectively, are well, with rates after operation: 2 plus, 1 plus, and 5 plus.

Our experience agrees with that of others in emphasizing the importance of the general clinical observation as control of this objective test, the basal metabolism. This does not diminish the value of the information given by the basal rate, any more than clinical examination lessens the necessity of the routine use of the thermometer or the leucocyte count. It is the best guide in disturbance of the thyroid secretion. Generally speaking patients with hyper-

TABLE III

CASE	SEX	AGE	HT. CM.	WT. KG.	OX. VOL. P. 10M.	CAL. P. DAY	NORM. CAL. BM PER D	% VAR.	X-RAY TREATMENT
1	M	30	164	56.9	2838	1987	1467	35+	May 18, goiter, tremor, p. 90, no exoph.
				55.2	2272	1591	1444	10+	June 10, rest, p. 70, pulse press. 60
				56.	2609	1826	1455	25+	July 20, rest and sed. brom., pulse 70
				54.6	2398	1679	1435	17+	Sept. 30, had 8 x-ray treatments, improved
2	M	22	174	51.4	2901	2030	1495	36+	Nov. 9, 1920, p. 104 hyperthyr. and funct. heart
				60.3	2295	1601	1611	1–	June 11, 1921, weekly x-ray. Well, at school
3	M	24	182	68.3	3844	2688	1754	53+	Oct. 29, 1920, p. 185, severe exoph. goiter
				67.3	3471	2324	1740	33+	Dec. 1, 1920, 3 x-ray treatments in Nov. In business college
				70.5	3006	2106	1784	17+	Jan. 11, 1921, 3 x-ray treatments per mo. In business college
				71.4	3334	2334	1796	30+	Feb. 1, worse. 3 x-ray treatments per month. In business college
				72.4	2993	2096	1810	16+	March 8, improved. Weekly x-ray. In business college
				70.1	2930	2052	1778	15+	April 13, p. 75, weekly x-ray. In business college
				70.5	2974	2082	1784	16+	May 3, p. 78, weekly x-ray. In business college
				71.	2877	2014	1791	13+	June 16, p. 60, weekly x-ray. In business college
				71.	2491	1744	1791	3–	July 15, well except for exophthalmos
				70.5	2589	1812	1784	1+	Aug. 5, p. 60
4	F	32	165	49.1	2339	1638	1281	28+	Three mo. previous BM was 67+
5	F	29	162	46.4	2363	1655	1263	31+	Jan. 29, pulse 150, severe ex. goiter
				51.6	1203	843	1313	36–	June 6, p. 75, weak, x-ray discontinued
				50.2	1741	1219	1299	6–	July 19, no treatment, well
6	F	35	163	71.1	2144	1630	1473	10+	Nov. 12, 1920, hyperthyroidism, mild
				72.9	1987	1391	1485	6–	Jan. 21, x-ray treatment. No symptoms now
7	F	49	170	74.8	2125	1488	1503	1–	March 5, still well and gaining weight
				61.1	1532	1073	1324	19–	Feb. 13, dysthyroidism, p. 106, exophth
				59.5	2020	1415	1309	8+	June 14, x-ray treatment, pulse 80, improved
				62.5	1837	1286	1352	5–	Oct. 10, well. (Thy. ext. made worse, Feb.)

thyroidism with rates under 30 plus can be treated by roentgen rays as successfully as by surgical means, and the time needed for the raying is not excessive, as it is apt to be in more severe cases. The ray is invaluable as a follow-up when partial thyroidectomy has not entirely reduced the excessive secretion to normal. Surgery in severe cases must be cautious, but ligations must be followed by partial thyroidectomy before the establishment of collateral circulation, which means within three or four weeks. The basal rate should be measured and the operation done while the rate and pulse are yet declining. Frequent basal metabolism tests are necessary with present knowledge to determine the time of operation after preliminary rest in bed, and whether ligations or a primary thyroidectomy are safest, although the general clinical picture, with particular reference to the cardiac reserve, must be a controlling factor.

Case 1, Table IV, referred by Dr. Weir, had so low a basal metabolism, relieved by giving thyroid extract, that it is reasonable to suppose her toxic symptoms were due to a glandular unbalance associated with pregnancy. There was a lag between the restoration of a normal basal metabolism and her symptomatic relief, also present in Case 2. This woman had been suffering from the disturbances of the climacteric, weakness, irritability, fainting spells, and complained most of a paronychia that was painful and intractable, all symptoms aggravating in cycles of more or less four-week periods. The first basal rate was measured on an upgrade, 5–, the next during the depressed period was 17–. Feeding thyroid extract she feels better than she has for four years, the paronychia has not recurred in 5 months, she sleeps soundly and does her housework cheerfully. The rate is 26 plus, but her age is fifty, and the health is the proper guide as to what is normal for her, although her heart is being watched by her physician. Case 3 referred for metabolism by Dr. Winters is similar; menopause disturbances, premature in this case, associated with mucous colitis. She was given thyroid and ovarian extract, has gained weight, been relieved of her colitis, and sexually is returning to normal. The last two cases are included to guard against overenthusiasm. Case 4 has an eczema worse at menstruation, 5 is undergoing the menopause with considerable distress, palpitation tachycardia, suggestive of thyroid hypersecretion. Neither showed thyroid disturbance demonstrable by change in the basal metabolism.

TECHNIC

The method of making the estimation of basal metabolism is essential. The use of apparatus that has not the weight of approval of the men with the most experience might invalidate the work of those beginning to make the test, and tend to bring the test itself into discredit. The Tissot apparatus gives information that is necessary in the general investigation of metabolism, but to the clinician has no advantages to offer, while the requirement of a trained gas analyst and the factors for time and cost are insuperable obstacles outside of large supported clinics. On the other hand extreme portability is not needed, the patients too ill to come to the laboratory, as Bailey[13] says, are not the type of case in which basal metabolism determination is of value. The Benedict Portable Respiratory apparatus[14] seems to have all the simplicities possible to

TABLE IV

CASES SHOWING ENDOCRINE UNBALANCE

CASE	SEX	AGE	HT. CM.	WT. KG.	OX. VOL. P. 10M.	CAL. P. DAY	NOR. CAL. BM PER D.	% VAR.	
1	F	26	165	51.1	1274	892	1327	33–	Feb. 3, preg. 4 mo., depressed, weak, persistent vomiting
				51.1	1908	1336	1327	0	Feb. 8, taken thyr. extr., same symp., by Feb. 10 felt well; BM
									9– on Feb. 19; remained well to term
2	F	50	163	67.9	1719	1203	1372	5–	July 6, feeling fair, upgrade
				70.5	1667	1167	1397	17–	July 25, weak, fainting spells
				69.3	2000	1400	1386	1+	Aug. 1, thyr. extr. daily, feels same
				67.4	1812	1268	1368	7–	Aug. 30, felt improved since 20th
				70.9	2736	1770	1401	26+	Oct. 25, feels better than for four years
3	F	34	156	44.1	1285	900	1207	25–	Aug. 22, mucous colitis, menopause
				44.5	1384	969	1211	20–	Oct. 4, thyr. extr., improving
				46.4	1768	1124	1229	9–	Nov. 4, thyr., feels well, colitis gone
4	F	30	161	70.2	2017	1412	1484	5–	Sept. 2, before menstruation
				71.1	2043	1430	1493	3–	Sept. 13, after menstruation
5	F	40	165	58.5	1963	1374	1333	3+	Menopause, palpitation, asthenia

careful work at present. It is portable in the sense of being movable about a hospital, but is best kept in a metabolism room to which patients may be brought on a litter if bed-ridden.

Roth[15] in a paper on the use of the Benedict apparatus says the chances of error lie chiefly in improper management of the subject. The patient should see the apparatus the day before the test, when it should be explained to him, lest fear of an unknown test, of suffocation, or excitement raise the oxygen consumption. He should come to the laboratory, or be brought there, in the morning, fasting, having had no food including tea or coffee since the previous evening. The metabolism room should be quiet, and no one allowed in during tests except the operator and nurse. The patient is placed in a recumbent position, with pillows as needed, in the darkened room, for half an hour before the test. The position must be comfortable so that movements, restlessness, or changes of position will not add to heat production, and the head must be high enough to allow the saliva to be swallowed easily with the mouthpiece in. When nervous tension or apprehension is unavoidable, after a short trial breathing into the apparatus the patient is best dismissed and the test made another day. Cases with severe thyrotoxicosis are unable to repress movements. Rarely it is impossible to get sufficient cooperation to make the test. The age of the patient to the nearest year, height without shoes in centimeters, weight to tenth kilo are noted, the weight to be taken at the time of the test, and the barometer is read. The temperature is taken to rule out fever.

Fill the spirometer three-fourths full of oxygen and start motor. Test for leaks. Place clamp on the patient's nose, have him try to breathe through the nose. Adjust the rubber mouthpiece attached to the three-way valve, inside the lips, outside the teeth, raising or lowering the support arm and changing the angle so it rests easily in the mouth. Tell the patient to breathe naturally and to avoid forced expiration. Cover his eyes with a light cloth. Turn the three-way valve at the end of an expiration. Read the temperature of the spirometer bell. Take patient's pulse. When the breathing has become regular, the excursions of the indicator showing a small loss at the end of each expiration, take readings as Emmes directs: Write the minute by the watch (the minute and second hands set together), then note the reading of the spirometer at the height of a normal expiration, immediately note the second by the watch, and write both beneath the figure for the minute. Repeat such readings several times a minute for two or three minutes, and again for two or three minutes just previous to the end of the test (10 min.). Take the pulse and respiration in the interval.

Subtracting the time readings, (the seconds conveniently written as decimal fractions of a minute) and the corresponding readings of the volume of oxygen in the spirometer taken at the start, from those taken at the end of the test, the number of c.c. of oxygen retained in a period of minutes is obtained, which may be computed as an average for ten minutes, averaged from the sum of the total number of readings, from both periods of the test. To reduce this volume to normal temperature and pressure of zero Centigrade and 760 mm. barometric pressure, this figure is multiplied by a factor from tables for the reduction of

gas volumes at different pressures and temperatures.[16] Should the temperature of the spirometer bell have risen during the period of the test add for each degree rise 1.8 c.c. to the observed volume before correction.

To obtain the basal heat production for 24 hours from the corrected volume of oxygen consumed per 10 minutes, this figure must be divided by 1000 to reduce to liters, multiplied by 6x24 (time factor) and by the caloric value of a liter of oxygen, 4.825 for an assumed respiratory quotient of 0.82, generally taken. $6\times24\times1/1000\times4.825 = 0.6948$. 0.695 times the figure for the corrected volume of oxygen consumed in 10 minutes gives the basal heat production per 24 hours in calories.

If the respiratory quotient of 0.85 is assumed for the Portable apparatus as is done by the Nutrition Laboratory[17] the caloric value for the oxygen is 4.863 and the factor for the daily basal heat production from the c.c. oxygen per 10 minutes is 0.7003.

Having found the patient's basal metabolism in calories per day, there remains to determine the normal basal metabolism of the age, sex, height and weight of the patient. For this there are two methods of procedure. Both the Aub and DuBois normal standards, and the normal prediction tables of Harris and Benedict agree closely for adults, particularly between the ages of 20 and 40. On account of the small number of normal women over 40 measured, on which these analyses are based, the variation is greater for these older women. Both standards are derived from the same statistics. "For the pres-

REPORT OF BASAL METABOLISM DETERMINATION

PATIENT'S NAME DATE
ADDRESS REF. BY DR.

Average of readings of oxygen consumed per 10 minutes
Period A c.c.
B c.c.
C c.c. — average c.c.
add 1.8 c.c. for each degree rise in temperature c.c.
Temperature spirometer bell,
beginning A B C Barometer mm.
ending A B C
Factor to correct volume oxygen to 0 and 760 mm. 0.
Corrected volume oxygen per 10 minutes c.c.
Calories per day, basal rate calories.
(RQ 0.85, factor 0.7003; RQ 0.82, factor 0.695.)

Age Height cm. Weight lbs. kg. est. less kg. for clothes.
Harris-Benedict tables normal prediction:
Factor, body weight and sex .....
Factor, stature, age and sex ..... ——————(add)
Estimated calories per day (normal) .....
Calories per day, observed, (above) .....
Percentage variation from normal, basal metabolism

Aub and DuBois standards:
Body surface area, (height-weight chart) in sq. meters.....
Calories per day per square meter, for age and sex, ... ——————— (multiply)
Calories per day, basal heat production .....
Calories observed, daily basal metabolism (above) .....
Percentage variation from normal, basal metabolism .....

Notes, cooperation and behavior
Pulse A B C Respiration A B C temp.
Clinical notes

ent persons who are presumably in good health are taken as normal individuals."[18] The standard for girls from 12 to 17 years old has been determined by Benedict and Hendry.[19] It averages 1250 calories per day irrespective of age, the accuracy is only slightly greater when weight is considered. These tables, as well as formulae for other children and for infants, are most conveniently found for reference in Carpenter's "Tables, Factors and Formulas for Computing Respiratory Exchange, etc.," which in small compass furnishes all the data needed for basal metabolism estimation.[16]

From the DuBois height-weight chart the body surface area in square meters is obtained, this figure multiplied by the average normal calories per square meter per day for the age and sex gives the normal 24-hour basal heat production. Comparison with the observed rate shows whether the latter is higher or lower, "plus" or "minus," and the percentage variation is the basal metabolic rate.

If the Harris-Benedict standard basal heat production is used the tables in "A Biometric Study of Basal Metabolism in Man"[20] (also given by Carpenter) give factors for the weight, and for the age and height, of the sexes, two figures which added give the figure for the calories of basal metabolism per day for the normal.

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A NEW TYPE OF RECORDING SPIROMETER*

By R. Burton-Opitz, M.D., New York

THE type of spirometer which has been made use of by me in this laboratory, registers the volumes of the respiratory air as a continuous line upon the smoked paper of a kymograph. Moreover, since the action of its different parts may be reversed at any time, it may be employed to record a practically unlimited number of respiratory cycles. The resistance resident in its different parts is so slight that the subject of the experiment scarcely perceives any hindrance to the flow of the respiratory air. A very simple change in the adjustment of this apparatus enables the experimenter to register solely the volume of the tidal air or solely that of either the inspiratory or expiratory air.

The most essential part of this instrument is a cylinder which is placed horizontally and gives lodgment to a piston of hard rubber. The excursions of the latter are registered upon the smoked paper of a kymograph (Fig. 1). The cylinder (C) is made of brass and measures 30 cm. in length and 12 cm. in diameter. Its internal surface is ground absolutely true with pumice powder. Piston (P) is adjusted to move in a horizontal direction through this chamber without being able to form contact with the covers D and D_1. In order to decrease its weight and to prevent all leakage of air, the thickness of the central area of its rubber disc has been reduced to about 0.5 cm., while the edges of this plate have been permitted to retain a breadth of 1 cm. This rubber disc is held in its proper position by a steel rod (R), measuring 2 mm. in diameter and 58 cm. in length. The ends of this rod rest in the central orifices of the covers of the cylinder. The internal surfaces of covers D and D_1 are equipped with three horizontal rods (E_1), each of which measures 4 cm. in length. Their purpose is to restrict the lateral excursions of the piston, so that its surfaces cannot form contact with those of the covers. By this means, two dead spaces are formed in the ends of the cylinder which give lodgment to the orifices of two tubes, designated in the figure by the letters B and B_1. A strong rod is fastened in a horizontal direction to the posterior surface of the cylinder. It serves as a means of adjusting the entire apparatus securely in the clamp of an upright stand (Fig. 2).

The aforesaid tubes B and B_1 possess an internal diameter of 2 cm. and an outside diameter of about 2.2 cm. They are curved and descend obliquely along the opposite sides of the cylinder to the lateral outlets B and B_1 of valve V. The latter consists of a capsule of brass which is fastened to the floor of the cylinder. It contains a rotating disc, measuring 7 cm. in diameter and 3 cm. in height. Two U-shaped tubes, possessing a diameter of 2 cm., pierce its mass in opposite directions to one another. The vertical axis F traversing

*From the Physiological Laboratory of Columbia University.

Mr. Joseph Becker, 437 W. Fifty-ninth street, New York, has agreed to manufacture this instrument according to specifications.

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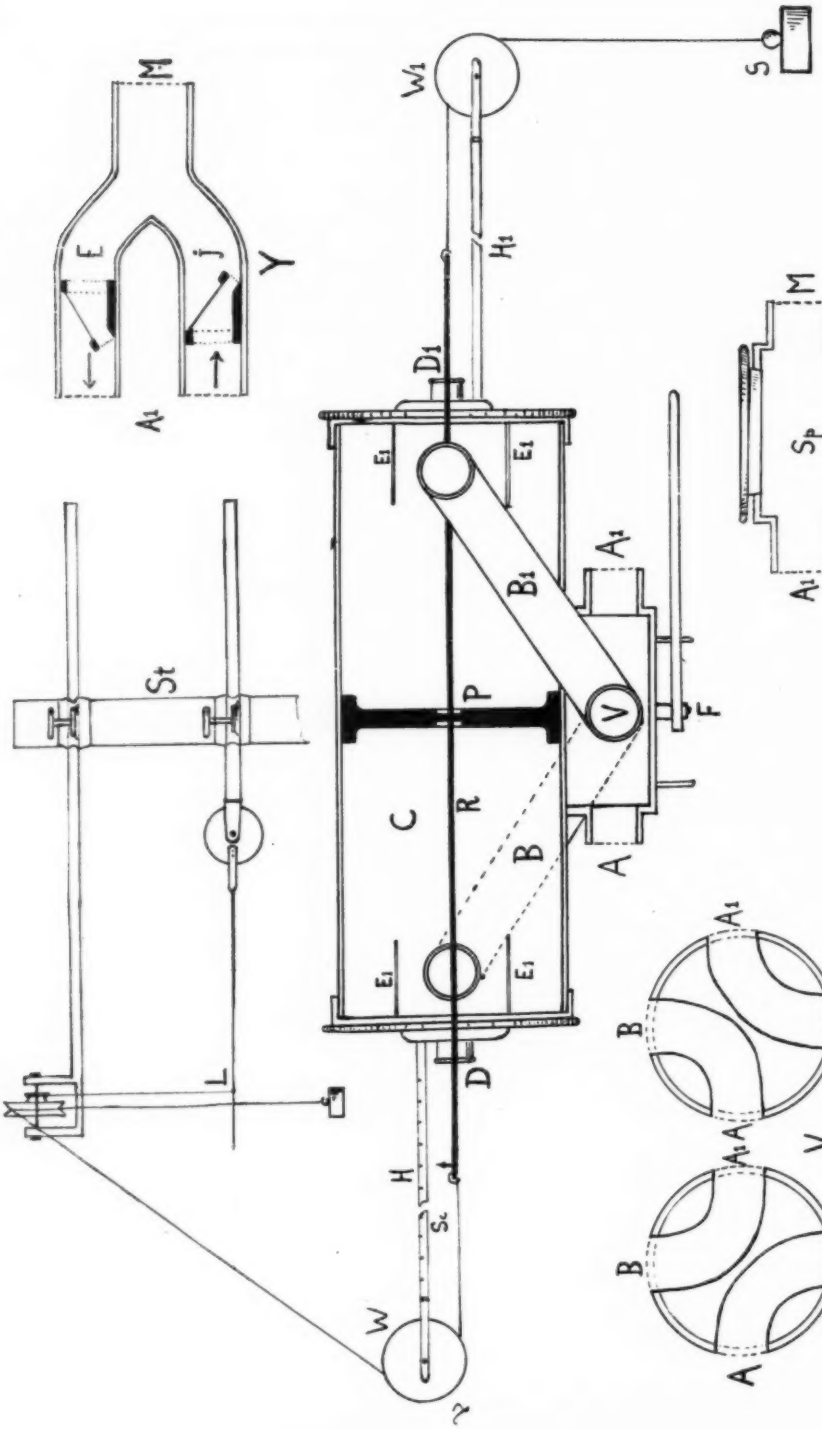

Fig. 1.—Recording spirometer: *C*, cylinder with piston and recording attachments; *Y*, inspiratory and expiratory valves; *V*, valve for changing the direction of the current of air; *Sp*, ether chamber.

its center serves as a means of changing the position of these tubes, so that the air entering through orifice A_1 may be diverted at any time either into tube B or tube B_1. Two small metal projections upon the floor of the capsule containing the disc indicate the positions which the handle of the axis must assume in order to cause the air to flow alternately in these directions.

If the entering air is diverted from tube A_1 into tube B, the piston will be made to move from left to right. As soon as it has reached its extreme position against the thin rods E_1 attached to cover D_1, the position of the rotating disc is quickly changed. Orifice A_1 is thereby brought into communication with tube B_1. The air now rushes into the compartment below cover D_1 and causes the piston to move from right to left. The rotating disc is again reversed as soon as the piston has attained its extreme left position. The air escapes from the cylinder through orifice A.

The reversal of the rotating disc consumes only about 0.25 second, and hence, if necessary a continuous stream of air may be made to traverse this instrument for almost any length of time. As has been stated above, the capacity of the cylinder is 2000 c.c. Accordingly, from three to four ordinary inspiratory or expiratory blasts of air may be directed through it before the disc need be rotated to allow another 2000 c.c. of air to enter. The same procedure is followed in measuring the complemental air and the vital capacity. Furthermore, it will be evident from the figure that the air may also be made to enter through orifice A and to escape through orifice A_1.

In order to be able to measure the inspiratory and expiratory amounts of air separately a Y-shaped tube has been constructed which may be attached to orifice A_1 as well as to orifice A. The short limbs of this tube possess an internal diameter of 2.3 cm., so that their ends may be pushed over the inlet tube of the rotating disc. Each limb contains a valve, possessing in general the form of a slanting trap-door. Its narrow frame of brass fits snugly into the tube, while its orifice, measuring about 1.5 cm. in diameter, is closed by a round plate of aluminum, hinged above and slightly weighted below. Thus, the quick closure of this valve is insured not only by the slanting position of its metal disc, but also by the fact that the lower margin of the latter is equipped with a slight weight.

Naturally, these valves must be adjusted in such a manner that they open in opposite directions to one another. Thus, if it is desired to direct solely the inspiratory air into the cylinder to be registered, that limb of the Y-shaped piece of tubing must be connected with tube A_1 which gives lodgment to the valve opening towards the mouth-piece M (J). At this time, the limb (E) containing the valve opening away from M, is permitted to project free into space. The expiratory air now escapes through this limb without being registered by the piston. Contrariwise, if it is our intention to ascertain the volume of the expiratory air, the tube containing valve E must be connected with tube A_1 of the rotating disc, while tube J is permitted to project free into space. It need scarcely be mentioned that the position of this Y-tube may also be reversed, thereby bringing the valves J and E closer to the mouth of the subject. Their action is then reversed.

The free end of the Y-tube is connected by means of a rubber tube with a facial mask (*M*), such as is commonly employed in etherizing patients. An even more efficient appliance is the gas-mask, because it may be applied more firmly to the surface of the face. The internal diameter of this rubber tube should equal that of the metal tubing used in the construction of the spirometer. It need scarcely be mentioned that this spirometer may also be connected with the lateral of a tracheal cannula, enabling us to register the amounts of air breathed by an etherized animal. Lastly, it may be employed to record the amounts of air delivered by an artificial respiration machine. The trachea of the animal should then be connected with orifice A_1 of the rotating disc, while the tube conveying the air from the pump should be attached to inlet *A*.

In order to be able to continue the narcosis for a long period of time, outlet A_1 of the rotating disc may be equipped with a small metal chamber

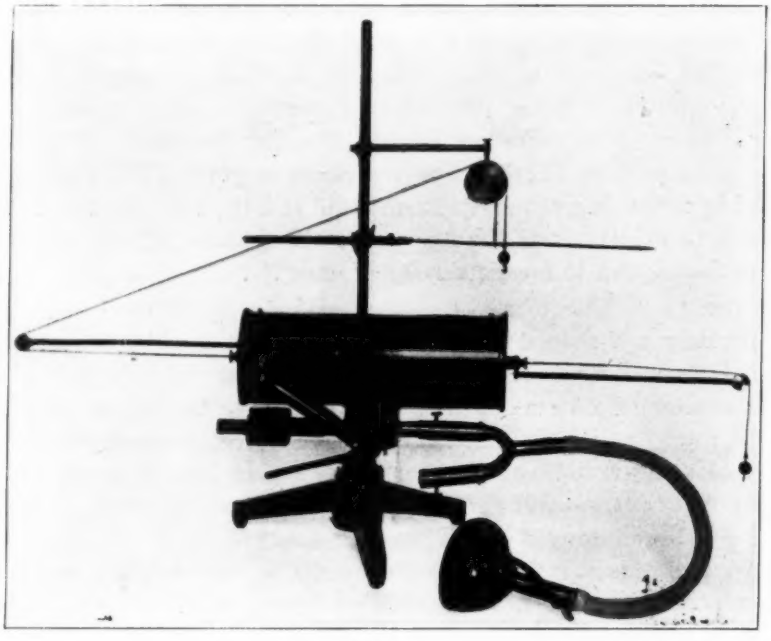

Fig. 2.

containing a sponge which may be moistened from time to time with ether (*Sp*). This chamber may be bulbular in shape, measuring about 5 cm. in diameter, or square with sides measuring about 5 cm. in length. Its cover should be made to fit very closely so as to prevent all leakage of air.

The volumes of the respired air are registered by means of a writing lever (*L*) which is connected with the end of the piston-rod (*R*) by means of a thread. This thread rests in the groove of wheel *W* attached to rod *H*. It is then wound twice around a second wheel placed directly above the tip of the writing lever. Its end is permitted to hang free in space weighted with a 3 gram weight. The second wheel measures 7.5 cm. in diameter, and is connected with a third wheel, rotating upon the same axis. The latter possesses a diameter of 2.5 cm. Its groove gives lodgment to a thread which is fastened to

the writing lever near its tip. This arrangement decreases the excursions of the writing lever considerably, so that the movements of the piston-rod which normally measures 22 cm. in length, yield a curve only 10 cm. in height. Accordingly, two tracings may be made above one another upon paper possessing the usual breadth of 25 cm.

The writing lever consists of a delicate beam of wood, measuring 28 cm. in length. Its weight is accurately balanced by the weight *G* attached to the other end of the piston rod. Inasmuch as rods *H* and H_1 are movable, the recording lever *L* may also be connected with the right end of the piston-rod, while weight *G* is attached to its left end.

Another way of recording the volumes of the air respired is to attach a small weight to each end of the piston-rod and to equip one of these with a delicate writing lever which may be held against the paper of the kymograph by a horse-hair weighted at its lower end. Lastly, the volumes of the air may be read off directly from a scale (*Sc*) attached to the guard-rod *H*.

Possibly the simplest way of calibrating the cylinder of this spirometer is to attach a large rubber tube to orifice *A* of the rotating disc and to permit its

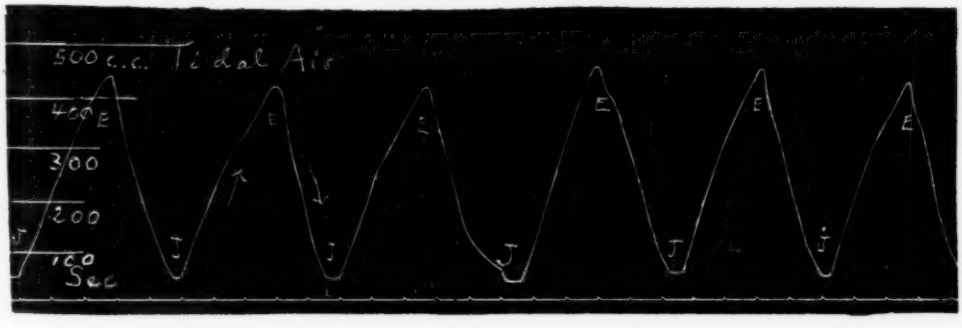

Fig. 3.

free end to project into a vertical graduated glass tube filled with water. If valve *Y* is now adjusted to yield only expiratory currents of air, the volume of each may be accurately ascertained by permitting this air to displace the water within the graduated tube.

If the facial mask *M* is connected directly with tube *A* or A_1 of the rotating disc, the writing lever *L* will register a series of successive up and down strokes which may be widely separated from one another at their bases by increasing the speed of the drum. Since the course of the air determines the direction of the movement of the piston, the upstroke may represent either the inspiratory or the expiratory phase. In other words, the direction of movement of the writing lever depends upon the position of the rotating disc. To illustrate this statement more fully, I have inserted in this place Fig. 3, in which the letters *J E* indicate the inspiratory period, and the letters *E J*, the expiratory period. The time consumed by these movements is indicated by the pointer of a Jaquet chronograph. This record serves at the same time as the abscissa for the curve of the volume of the respired air. If the height of these

lines is now compared with the record of the calibration of the cylinder, it will be seen that about 425 c.c. of air have been moved during each phase. Secondly, it is possible to detect all minor variations which have developed in the course of each inspiratory or expiratory movement. Thus, these curves reveal not only the time relationship between the successive cycles, but also certain sec-

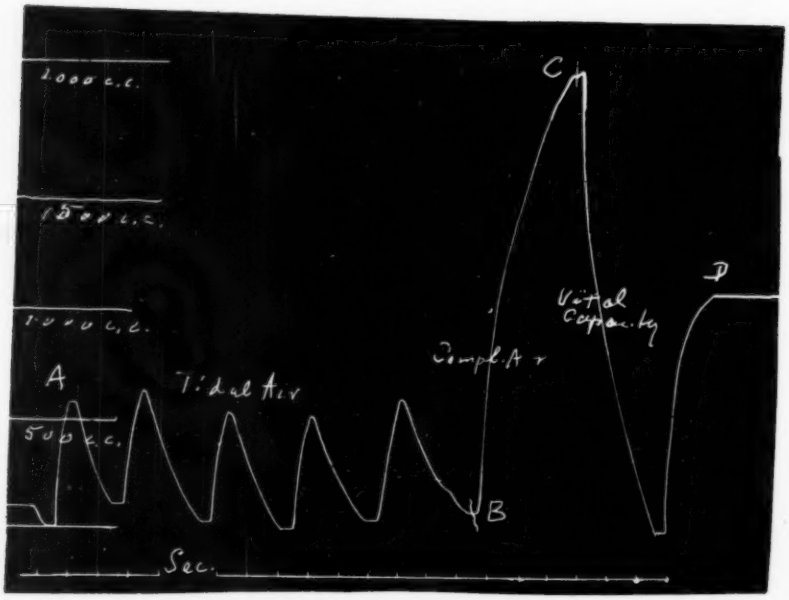

Fig. 4.

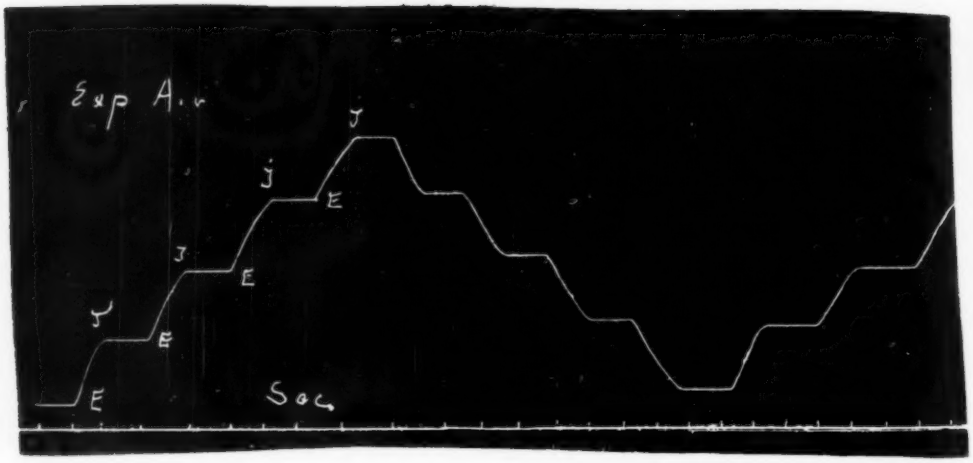

Fig. 5.

ondary changes in each indicating brief variations in the rapidity of the respiratory movements.

Fig. 4 is intended to illustrate the records obtained when the determination of the tidal air is followed by a determination of the complemental air and vital capacity. It will be seen that the volume of the complemental air (*BC*)

amounts in this instance to 1800 c.c., while the vital capacity (*CD*) equals 3200 c.c.

Under the same general conditions, the insertion of the expiratory valve yields a curve such as is represented in Fig. 5. The expiratory phases are here indicated by the letters *E J*, while the inspiratory phases (*J E*) are registered as straight lines, because these currents of air are not permitted to traverse the cylinder. Contrariwise, the interposition of the inspiratory valve causes the inspiratory blasts of air to be recorded but not the expiratory ones. The general character of the curves is the same in both instances.

A SELF-FEEDER FOR RATS*

By Ralph Hoagland, B. Agr., Washington, D. C.

ONE of the most important pieces of equipment needed in carrying on quantitative feeding tests with rats is a self-feeding device that will allow the rat free access to the feed and yet prevent his wasting it or contaminating it with his excrements. The writer has devised a feeder which meets the above requirements satisfactorily and a description of the same is offered for the benefit of any one interested in such a piece of equipment.

Fig. 1 is a scale drawing of the feeder. It consists of three separate parts designated as: *A*, receptacle for waste feed, also serving as base for feeder; *B*, *C*., vestibule and feed hopper; *D*, cover to feed hopper. The feeder is made of heavy-coated bright tin and one-eighth inch mesh galvanized-wire screen. The respective parts of all feeders are interchangeable. A good tinsmith can make one of the feeders in approximately two hours.

The feed hopper will hold approximately 100 grams of feed, depending upon its character. When the ration is relatively low in fat the feed will drop down as the rats eat, but when the fat content is high and the feed rather sticky, it is necessary to knock down the feed once daily. At present the writer is adding ten per cent of fat to the rations and the feeders are examined daily to see that ample feed is available. The feed hopper is filled with feed and then weighed. At the end of a week the feeder is freed from any adhering feces and weighed. The loss in weight represents feed consumed, provided there has been no wastage. The screen floor to the vestibule catches the feces so that they do not contaminate any feed that may have fallen into the base of the feeder.

The vestibule to the feeder is larger than necessary for a young rat weighing 40 to 50 grams, but it will accommodate a mature animal weighing 250 to 300 grams. However, the feeder has given satisfaction with small rats as well as with large ones, so that only one size has been used. In fact, the

*From the Biochemic Division, Bureau of Animal Industry, United States Department of Agriculture, Washington.

Received for publication, December 1, 1921.

large rats have been the worst offenders in pulling down feed into the base of the feeder.

For the most part, the rats do not pull out any considerable quantity of feed into the waste-feed receptacle, particularly if the ration is adequate, and

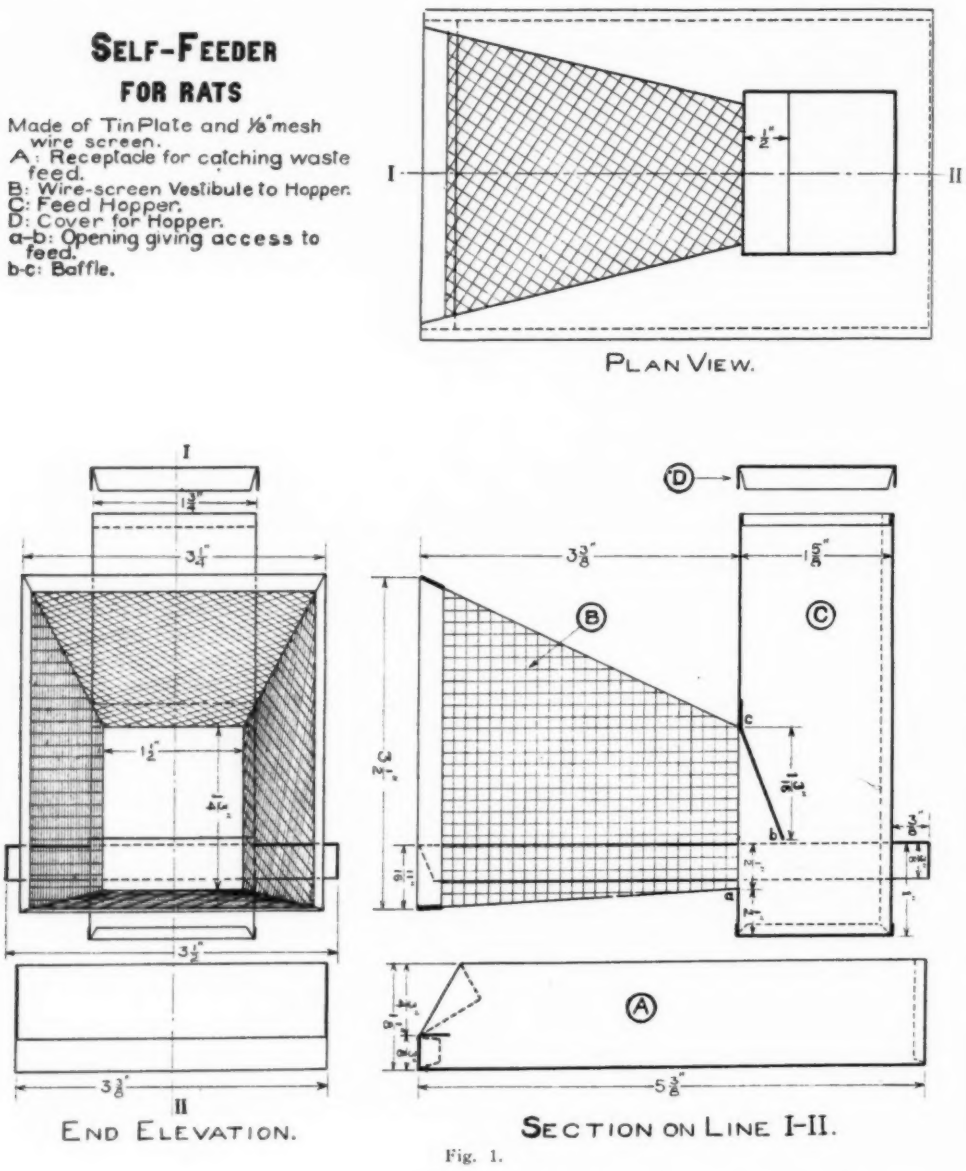

Fig. 1.

it is only occasionally that a rat will pull a little feed entirely out of the feeder on to the floor of the cage. In our feeding tests, each feeder is examined daily, feces being removed from the floor of the vestibule and any feed in the waste-feed receptacle, unless unclean, is returned to the hopper, which is tapped to knock down the feed within reach of the rat. The feeder is weighed at the

end of the week and the feed remaining in the hopper is transferred to a clean feeder, which is filled with additional feed and weighed. The dirty feeder is cleaned and then sterilized in live steam. A reserve supply of approximately one-half the number of feeders in use is maintained so as to facilitate operations.

In the light of several months' experience with the self-feeder described (approximately eighty are now in use), the following slight modifications are suggested: (1) Increase the depth of the waste-feed receptacle (*A*) from 1⅛ to 1½ inches, so as to provide more storage room for waste feed; (2) modify the baffle plate (b-c) so that it can be raised or lowered as desired in order to prevent rats from pulling feed out into the vestibule.

REMOVABLE WATER-BATH TOPS FOR PARAFFIN EMBEDDING AND LOW-TEMPERATURE EVAPORATION*

By Oscar T. Schultz, M.D., Chicago, Ill.

THE writer described in 1917† a rectangular electric water-bath for serologic work. There are now on the market a number of baths constructed after the general plan there described. The need having arisen in our own work for a bath for paraffin embedding, it appeared possible to devise a top which would transform the serologic water-bath into a paraffin bath at a very considerable saving of space as compared with the usual incubator or cabinet form of paraffin embedding oven. With this object in view we have had made according to our specifications a removable top to fit the small 9 by 4½ by 5 inch water-bath. The top (Fig. 1) is made of sheet copper and has three cylindrical, sheet copper depressions, 2¾ inches deep by 2¼ inches in diameter, each of which holds a beaker of stock size. There are also five depressions 1¾ inch deep by 1 3/16 inch in diameter which take wide-mouth vials or square bottom test-tubes of standard sizes. A tubulature is provided for a thermometer. Thus arranged, a bath (Fig. 2) which requires an extreme table space of only 12 by 6 inches has been found ample for the pathologic work of a 475-bed hospital in which all tissues removed at operation are routinely sectioned.

It may not be amiss to describe the method which makes possible the running through of such an amount of tissue with the minimum of trouble and labor and with no danger of confusing specimens. Every specimen, as soon as it is received from the operating room, is given a surgical pathology number, the data relating to the specimen are entered upon the proper record forms, the gross material is examined fresh, and then it is placed in the fixing fluid. After fixation and after the blocks of tissue for microscopic examination have been trimmed and are ready for dehydration, a small paper label bearing in pencil the number of the specimen is attached by means of a small drop of melted

*From the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital. Received for publication, Dec. 20, 1921.

†Schultz, O. T.: An Electrically heated, Constant Temperature, Water-Bath for Serologic Work, Jour. Am. Med. Assn., 1917, Nov. 1, lxix, 1521.

gelatin to the flat side of the tissue block opposite to the side from which the sections are to be cut. After allowing the gelatin to harden for a moment or two, the tissues are placed in the first dehydrating alcohol. In this way all the blocks from the material of a single day are handled together and are run through the various dehydrating and clearing fluids and into the embedding bath. A slip of paper which bears the specimen numbers of the tissues included in a given lot and the number of blocks from each specimen is carried along with the tissues. After embedding in paraffin, the specimen number can be read through the layer of paraffin which covers the small label on the reverse side of the specimen; this number is written in pencil or ink on the fiber block on which the tissues are mounted for sectioning. The individual blocks of

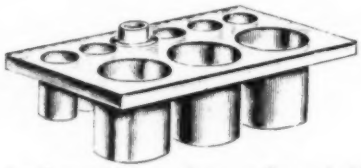

Fig. 1.—Removable top for paraffin embedding.

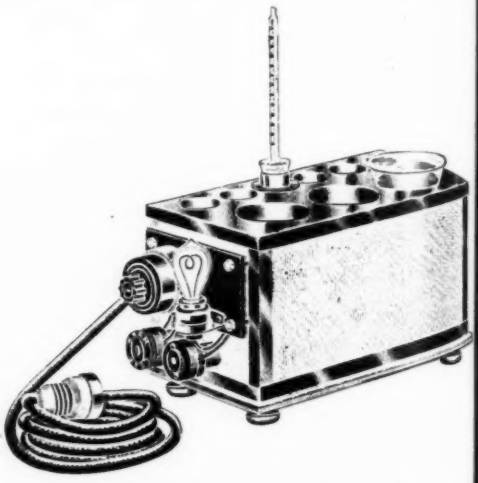

Fig. 2.—Water-bath complete for paraffin embedding.

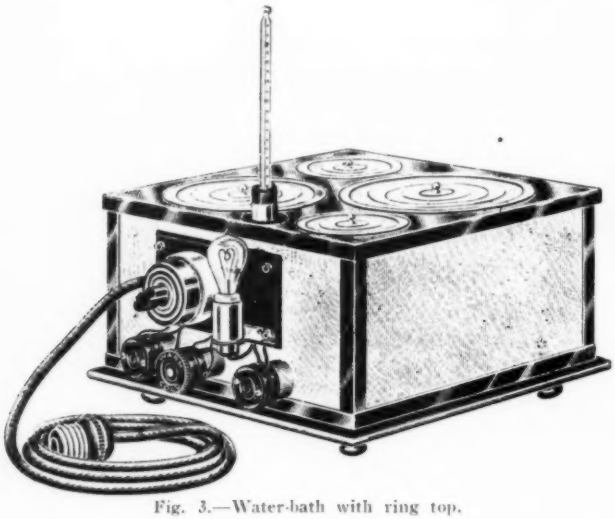

Fig. 3.—Water-bath with ring top.

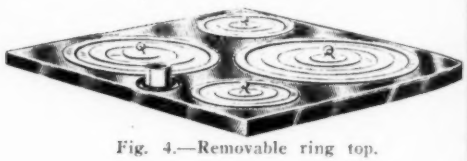

Fig. 4.—Removable ring top.

tissue from autopsies are not numbered, the entire lot from a single autopsy going through the various procedures together. Tissues which are to be examined for special investigative purposes are numbered like the surgical material and can be carried along with the latter. Very minute specimens do not have a label attached; they are handled separately and are embedded in the smaller receptacles which the paraffin bath provides.

In addition to the paraffin bath top, we have had made a removable ring top which transforms the 9 by 9 by 5 inch serologic bath into a bath for evaporation of volatile fluids at low temperature (Fig. 3). The top (Fig. 4) is made of sheet copper and has two openings 2 and 1/2 inches in diameter, one opening 4 inches in diameter and one opening 5 inches in diameter. Each opening is fitted with a series of concentric rings by means of which the size of the opening may be adjusted as required.

AN INJECTION METHOD FOR AIDING IN THE IDENTIFICATION OF TAPEWORM SPECIES*

By Raphael Isaacs, M.D., Cincinnati, Ohio

A SIMPLE method for visualizing the uterus in tapeworm proglottids, to identify the species, or for demonstration purposes, as used in the wards and laboratories of the Cincinnati General Hospital for the past five years, consists in the injection of the canals with India ink. A hypodermic syringe (1-2 c.c.), fitted with a fine needle, is filled with India ink. The segment to be

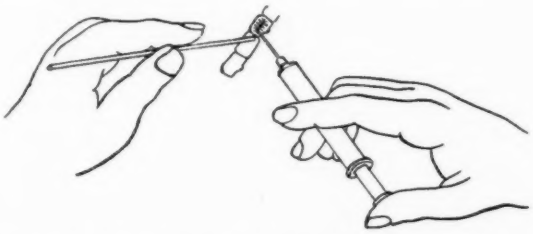

Fig. 1.—Method of holding and injecting tapeworm segments.

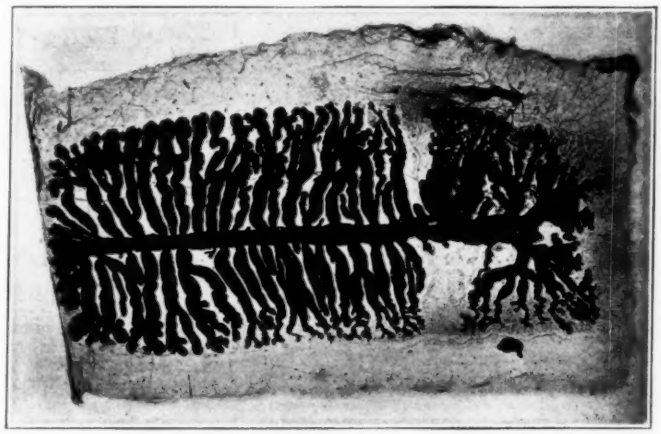

Fig. 2.

injected is held flat on a piece of glass by means of a wooden match stick or applicator, and the needle inserted into the substance of the fresh proglottid, near the lateral genital pore. With a little manipulation, one of the diverticulae of the uterus is easily entered, and the ink readily fills all the branches. Pressure between two glass slides brings out the details very clearly, and the

*From the Department of Internal Medicine, Cincinnati General Hospital, College of Medicine, University of Cincinnati.

Received for publication, December 17, 1921.

sparsely branched organ of T. solium is easily differentiated from the more abundant ramifications of T. saginata. The method is also applicable to other cestodes, and may also be used with preserved material although the results are not as complete as with fresh. Permanent preparations may be made by preserving the flattened segment in 10 per cent formaldehyde, dehydrating in alcohol, and, after clearing in xylol or carbol-xylol, mounting in balsam.

A METHOD FOR THE SEPARATION OF SPORE-BEARING ANAEROBES FROM OTHER SPORE-BEARING BACTERIA*

By J. Howard Brown, Ph.D., Princeton, N. J.

IN the isolation of anaerobic spore-bearing bacteria the strictly aerobic bacteria are easily disposed of because they fail to grow under strictly anaerobic conditions. The heating of mixed cultures or of a suspension of milk or feces for twenty minutes at 80° C. in sealed tubes is the common method of separating sporulating from nonsporulating organisms. If carried out carefully this method serves to kill the vegetative bacteria leaving only the spores to germinate when transplanted to suitable media. In our experience the separation of the anaerobes from the facultatively anaerobic spore-bearing bacteria was attended with considerable difficulty until the method to be described was employed. Many of the facultative anaerobes grow well under anaerobic conditions. Many of them are surface spreaders on the blood agar plate. The fact that under anaerobic conditions they may not present the same typical appearance that they do under aerobic conditions makes their recognition so much the more difficult. There may be nothing about their colonies to distinguish them from anaerobes growing in the same plate. We have frequently fished numerous colonies from an anaerobic blood agar plate and found them all to be facultatively anaerobic spore-bearing bacteria.

Various means of overcoming these difficulties have been tried. Preliminary incubation of mixtures under aerobic conditions to effect the germination of the spores of aerobes, followed by exposure to heat to kill the vegetative forms was attended by some success. However, much better results were obtained by incubation of the material in fluid media under strictly anaerobic conditions for several days, then heating the mixed culture for twenty minutes at 80° C. It was found that under strictly anaerobic conditions the facultative anaerobes did not produce spores, or at least none were found within the period of incubation of one week. Incubation must be long enough to permit the anaerobes to produce their spores. Florence (1922) has found that even under partially anaerobic conditions spore formation by a variety of aerobes and facultative anaerobes is greatly delayed. She says, furthermore, that "if transfers were made from cultures containing spores, the majority of spores carried

*From the Department of Animal Pathology of The Rockefeller Institute for Medical Research, Princeton, N. J.

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over did not germinate in the sealed tubes." We have not studied this phase of the problem, nor do we wish to state that no spores are formed by facultative anaerobes under anerobic conditions of growth. However, if certain of such spores do survive the process of anaerobic cultivation and the subsequent heating they are not present in sufficient numbers to cause serious trouble in the isolation of the anaerobes. After the vegetative forms have been killed by heat the mixture may be plated anaerobically at once or after germination of the spores in fluid media. For the preliminary anaerobic culture various selective media may be used to enhance the growth of various groups of anaerobic bacteria. For obtaining the growth of a large number of anaerobes of various kinds we have found it advisable to inoculate original material into at least the following three media under vaseline in test tubes, (1) cooked meat medium, (2) dextrose bouillon, and (3) sugar-free bouillon. Sterile tissue may be added to the last two if desired.

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Florence, Laura: The Influence on Spore Formation of Sealing Bacterial Cultures, Jour. Lab. and Clin. Med., 1922, vii, 199.

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EDITORIALS

The Diabetic Diet

THE principle of undernutrition in the treatment of diabetes, first elaborated by Allen and by Joslin, has, since 1914, been the most successful guide to intelligent therapy. Its advantages over previous methods have been demonstrated beyond cavil. By its use drugs and patent medicines have been largely eliminated and diabetic coma has been reduced to a minimum. Alkali treatment has passed largely into disuse. The average life of the diabetic subject has been increased by about two years. Joslin points out that with one million diabetic patients in the United States this treatment has added two million years in the aggregate to their lives. The hospital mortality rate has dropped from 28 per cent before 1914 to 2 per cent in 1920. This is due in large part to the prevention of coma but also to extraneous factors such as the more frequent hospitalization of early cases, for clinical observation. A diabetic under proper

treatment may now look forward in fair security to from five to seven years of life. Cases recognized early, such as those diagnosed during life insurance examinations have averaged twelve years of life. Under Joslin's care children now live fully three times as long with diabetes as they did prior to 1914, and the duration of the disease in the young adult is extended at least one-half. According to Allen an individual developing diabetes after forty or fifty may now look forward to completing his normal expectancy of life. The increased duration is not only common to all decades but is greatest in the decade with the most severe cases, namely the first.

Between 1914 and 1921 the Joslin and Allen treatments were used almost exclusively in this country. Since then considerable attention has been given to possible improvements in these diets. Joslin himself emphasizes the danger inherent in too strenuous fasting of the diabetic subject. In a recent article he states that although it may be desirable to lower the weight slightly, extreme lowering can hardly be advantageous. The ravages of a day's fast are not quickly replaced. A man on complete fasting loses 0.7 per cent of his body tissues each day. In a diabetic this cannot be quickly made up by overfeeding. One cannot give more than 5 or at most 10 per cent of extra food. Thus it may require as long as twenty days to make up for a single day of starvation, and the loss of weight entailed by a five days' fast might require from a hundred days to even a year for complete recovery. Weight must be sacrificed in order to get the diabetic sugar-free, but beyond this there should be no unnecessary loss. For each kilogram of body weight lost the patient loses approximately 126 grams of protein, 269 of fat and 15 of carbohydrate.

Thus the cost of undernutrition is great. Joslin recognizes its disadvantages but insists that even with these the ultimate results are greatly superior to those following overfeeding. He has modified his own preliminary treatment by omitting actual fasting whenever possible, and substituting partial fasting combined with a fat free diet. Frequently this suffices to free the urine of sugar. The danger from acidosis is diminished and patients leave the hospital sooner than after complete fasting.

Newburgh and Marsh in December, 1920, first published their observations on the treatment of diabetes with diets high in fat as compared with the Allen and Joslin diets. An apparently radical departure from the older methods and antithetical in principle, this method has on the contrary many points of resemblance. In both systems the principle of undernutrition is maintained. In the Allen or Joslin diets the carbohydrate intake is as high as is consistent with the individual's tolerance and the fat intake is relatively low. The reverse holds true in the dietary proposed by Newburgh and Marsh. The latter also adjust the nitrogen intake to a point not higher than is requisite to maintain nitrogenous equilibrium. A protein intake above the minimum is undesirable because of the glycogenic capacity and the specific dynamic action of the protein. Diabetics do not require more protein for the establishment of a nitrogen balance than do normal subjects. This, however, is not a point of distinct difference from the Joslin diet. Their modifications consist briefly in a reduction of the protein ration by about twenty grams, and the use of a fat and total

calory allowance somewhat higher than that of Allen or Joslin, but distinctly lower than that of Naunyn, Von Noorden and Petrén. They believe that by these modifications they can establish a higher tolerance or at least furnish a higher calorie intake, thereby preserving more satisfactorily the patient's nutrition.

Woodyatt has elaborated on the work of Newburgh and Marsh and has stressed the necessity of treating diabetes in terms of metabolism rather than of diet. It is true that protein, fat and carbohydrate are the substances ingested, but it is not these substances, as such, that find their way into the body tissues. Starch in the intestines and glycogen in the liver both appear as glucose in the blood. The protein of the diet no longer exists as such after digestion and absorption. Even the resultant amino acids are ultimately resolved into various components, of which glucose and beta-hydroxybutyric and acetoacetic acids form a large part. From 100 grams of carbohydrate the body, theoretically, metabolizes 100 grams of glucose. From 100 grams of protein the body metabolizes 58 grams of glucose and according to Woodyatt around 46 grams of fatty acids. One hundred grams of fat yield in the body approximately 10 grams of glucose coming from the glycerol and 90 grams of fatty acids. All of the foods of the diet except a small fraction of the proteins resolve themselves in the body into two substances, glucose and the higher fatty acids.

Carbohydrate tolerance therefore cannot be estimated simply from the carbohydrate of the diet. Estimations must also include the glucose derived from protein and fat, and the glucose arising in the body from endogenous sources.

Another fact on which Woodyatt lays great stress is the importance of the ketogenic balance in the body. Shaffer believed that acetoacetic acid itself is not easily burned in the body but that in combination with glucose or some substance intimately related to glucose an easily oxidizable compound is formed. Those substances which during metabolism give rise to acetoacetic acid and related acid bodies have been termed ketogenic. Those furnishing glucose which will combine with these acetone bodies are termed antiketogenic. Ketogenic substances are derived from fat and from certain amino acids such as leucin, tyrosin and phenylalanin. Antiketogenic substances are obtained, as we have seen, from glucose, protein and the glycerol fraction of the fat.

A balance must be maintained between the ketogenic and the antiketogenic substances. A preponderance of the former will cause acidosis. Thus if the glucose tolerance in an individual falls so low that one cannot administer sufficient glucose or antiketogenic substance to neutralize the ketogenic, acidosis will result. To prevent this the ketogenic intake must be decreased.

According to this conception we must estimate both sugar and fat tolerance in diabetics. The appearance of abnormal quantities of acetone, acetoacetic acid and beta-hydroxybutyric acid is the immediate result of the oxidation of certain fatty acids in the absence of a sufficient proportion of oxidizing glucose. For each individual there exists a definite ratio between the quantity of glucose oxidizing in the body and the maximum quantity of ketogenic fatty

acids that can be oxidized in the same time without the appearance of abnormal amounts of acetone bodies. Shaffer suggests that one molecule of glucose is necessary for the complete oxidation of one molecule of acetoacetic acid or one molecule of any higher fatty acid or amino acid capable of yielding one molecule of acetoacetic acid. Woodyatt assumes for clinical purposes that the ratio of higher fatty acids to glucose which, if exceeded, will lead to acidosis is about 1.5 to 1 (in grams). Wilder places this ketogenic threshold ratio at 2 to 1.

The rationale of dietetic management is then, according to Woodyatt, the adjustment of the glucose intake to within the carbohydrate tolerance and the adjustment of the fatty acid supply in relationship to the glucose supply so that the ketogenic balance is such that the ratio of 1.5 to 1 shall not be exceeded. In this way the patient not only becomes sugar-free but acidosis is insured against. The fat intake may be high provided it is not so high as to furnish an excess of fatty acids above that allowed in the ketogenic ratio.

Lusk stated in 1917 that in a fasting individual with much fat, little protein was consumed, but that when there was little fat much protein was burned and when there was no fat, protein alone yielded the energy of life. Woodyatt points out that the ingestion of fat may spare tissue fat and thus prevent the protein loss from becoming abnormally great. Fat ingestion may diminish the protein loss in those cases where the tissue fat has become too much depleted. If a fasting patient mobilizes and burns from 100 to 120 grams of fat the administration of an equal amount through the diet serves merely to conserve the tissue fat by that much. Why should the patient be compelled to draw from his tissues the fat that he might draw from a diet, particularly when in doing so he may increase his protein losses?

Woodyatt, in short, has attempted to arrange a diet in which the protein is adjusted to maintain nitrogenous equilibrium, the ketone products are completely oxidized, the available carbohydrate does not exceed the glucose tolerance, and which contains the greatest possible number of calories for the individual. In the compilation of such diets rather complicated mathematical formulae are necessary. This part of the work has been simplified by graphic charts which have been prepared by O'Hara, by Hannon and McCann, and by Wilder. With any of these the determination of the patient's optimal diet becomes comparatively easy.

Wilder emphasizes the importance of maintaining a decreased metabolic rate in cases under treatment. With a low sugar tolerance the diet must be carefully balanced so that the fatty acid-glucose ratio will not be so great as to cause acidosis. Reduction in the total metabolism will decrease the production of fatty acid molecules. One great advantage of caloric restriction probably lies in the consequent reduction of metabolic rate. It has been quite definitely shown that sugar tolerance in the diabetic may be increased by measures which depress the level of basal metabolism. Starvation causes a sustained fall in metabolism up to a point when, with extreme starvation, the rate tends to rise. Wilder suggests that when the fat stores are exhausted, the body proteins are called upon to provide the energy and the specific dynamic action of this cata-

bolized protein serves to elevate the metabolism. When this stage arrives in the severe diabetic, the effect on sugar tolerance is disastrous.

Fortunately a decrease in the metabolic rate may be obtained by undernutrition as well as by the actual fast. Wilder states that a low protein diet providing calories 20 per cent below the calculated caloric requirement will accomplish a depression of basal metabolic level of from 15 to 25 per cent. Thus the depression of the metabolism equals and balances the caloric deficit of the food, and both theoretically and practically patients may be maintained at constant weights on such diets. In maintaining a low metabolic rate the protein intake should only be sufficient to maintain nitrogen equilibrium so that its specific dynamic action will be minimized. Wilder accepts Newburgh and Marsh's conclusions that for an adult two-thirds of a gram of protein per kilogram body weight is sufficient.

In discussing the ketogenic-antiketogenic balance he points out that unless the calory and nitrogen values of the diet approximate the calory and nitrogen requirements of the patient, the results will show an unexpected imbalance in the ratio. Thus a diet may be accurately calculated and may contain the correct ketogenic-antiketogenic proportions, but if its caloric value is decidedly below the minimum requirement of the patient the deficiency will be made good at the expense of endogenous food stores, chiefly fat..

The dietary modifications above enumerated have not been unqualifiedly accepted by Joslin or by Allen, both of whom have had a volume of experience which adds value to their criticisms. Joslin remarks that just as experience with undernutrition has steadily yielded better results in his hands so, under certain conditions has the more liberal use of fats. He enumerates as the minimal requirements for the acceptance of any new method of treatment, first that the duration of the disease shall exceed the present average of 5.3 years, second that by the new treatment no deaths will occur during the first year of the disease, and third that the mortality from coma among patients treated in hospitals shall not exceed 1 per cent.

He remarks that a high fat, low carbohydrate diet is not new but represents the Naunyn type of treatment. The difference between the two lies in the relatively low quantity of protein and the reduction of total calories in the newer method. All past evidence indicates that the low carbohydrate-high fat ratio was responsible for the former high mortality from acidosis. He questions whether the reduction in protein and calories will prevent this mortality in the future. That coma was prevented in the series treated by Newburgh and Marsh is attributable to the low caloric value of the diet. Joslin points out that the dietaries used by Newburgh and Marsh contain a proportion of fat to carbohydrate twice that considered safe by Woodyatt.

Joslin particularly takes exception to the abnormal ratio between carbohydrate and fat. This ratio in the normal diet is about 6 to 1 while in the Newburgh and Marsh diet the proportion is almost reversed. A diet so low in carbohydrate and so high in fat palls upon a diabetic after several years of use. He points out that it has not been conclusively proven whether a patient acquires increased carbohydrate tolerance more readily by a high carbohydrate-

low fat ratio or by the reverse. "I cannot escape from the impression that a diabetic patient whose carbohydrate is once radically lowered and fat is radically raised suffers from the process and seldom regains a high carbohydrate tolerance."

Allen and Sherrill remark that the only actual modification suggested by Newburgh and Marsh is a reduction of the protein ration by perhaps twenty grams, and the use of a fat and total calory allowance somewhat higher than that of Allen and Joslin but lower than that of Naunyn, Von Noorden and Petrén. They do not accept the statement that since fat is burned in the fasting body the feeding of sufficient fat merely preserves the body fats. "Such suppositions defy old and new knowledge of both metabolism and diabetes." On a low carbohydrate-high fat diet the liver and the body tissues in general become stored with fat in preponderance over carbohydrate. The general overload of metabolism gradually lowers the carbohydrate tolerance. Glycosuria ensues and wastes some of the scanty store of carbohydrate. Then, the excess of fat in catabolism easily precipitates coma. However, the diabetic free from glycosuria can endure larger quantities of fat than those used by Newburgh and Marsh with no immediately serious acidosis. It is the later effects that must be guarded against.

Allen and Sherrill evidently consider loss of weight as an important feature of undernutrition therapy. This appears to be at some variance with the conception of Joslin. "To save body fat is contrary to the principle of undernutrition treatment, which is that the body weight must be reduced in proportion to the severity of the diabetes, as the only effectual means of keeping diabetic symptoms under control." According to their conception apparently, an increase in the caloric value of the food is not particularly to be desired even though this can be accomplished without the production of glycosuria.

They consider the cases described by Newburgh and Marsh to be in the main mild and therefore of the type that would not show early unsatisfactory results. They emphasize that the Ann Arbor workers by no means allow unlimited quantities of fat and that they follow closely the principle of undernutrition. It is only in cases in which this principle has been neglected that unsatisfactory results have been experienced. "They have at least not fattened a single severely diabetic patient, restored him to any lasting usefulness, or even kept him alive any long time on any high caloric ration. The one essential evil from which the undernutrition treatment gave relief was excessive fat feeding, and the benefits of such relief appear more strongly demonstrated today than they were at the time when this treatment was first proposed."

At the present time we have in this country two schools of diabetic therapy, both using the principle of undernutrition, but differing chiefly with regard to the value of the fat-carbohydrate ratio. Apparently logical theoretical considerations exist in favor of either method. The newer method will probably become popular if for no other reason than because of its apparent simplification with the charts and tables already published. Joslin has by a similar procedure made his treatment equally easy of execution. The minimum requirements enumerated by Joslin for the acceptance of the new method as an im-

provement must be met. Unsatisfactory results will, according to its critics, be rather late in appearing and time will therefore be necessary before convincing conclusions can be produced. In the meanwhile those who use the relatively high diet must do so with an understanding of the metabolic processes affected and of the potential dangers inherent in its faulty administration.

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—*W. T. V.*

A New "Tuberculosis Cure"

"GENEVA, July 22.—The British Red Cross, after careful investigation, has decided to purchase the vaccine treatment against tuberculosis originated by Henry Spahlinger, the Geneva biologist, and a contract for the sale has just been signed in London. The Spahlinger laboratories here will be continued, and others will be established, it is stated. A number of American patients, many of them advanced cases, and some given up by physicians, are now under treatment here, and all are showing improvement.

"The Spahlinger discovery was announced in Paris early in 1914. Little more was heard of it until after the war, but within the last year or two, it has attracted considerable attention, notably on the part of British officials. The serum can now be made as cheaply as the ordinary smallpox vaccine."

(Associated Press Item in Richmond Times Dispatch, July 23, 1922.)

Search through the pages of the Quarterly Cumulative Index of Current Medical Literature, since January 1, 1920, reveals but one reference to this method of treatment. This consists of an article by Henry Spahlinger of the Bacterio-Therapeutic Institute, Geneva, appearing in the Lancet, London, January 7, 1922.

Spahlinger's treatment utilizes either or both of two therapeutic principles depending on the nature of the infection. In acute or rapidly progressing cases passive immunization with special immune sera is employed. Active immunization with various special antigens is practiced in chronic afebrile cases, in non-pulmonary forms and in cases "predisposed to" tuberculosis.

Passive immunization is described as a form of progressive disintoxication. Different symptoms of intoxication are supposed to be due, not to varying manifestations of the same toxin, but to the action of different distinct toxins against each of which an antitoxin or "partial serum" must be prepared. These toxins are not merely the normal products of metabolism, but also substances elaborated by the microorganism as a means of defense. They are obtained experimentally by the use of virulent strains of bacteria "stimulated at definite intervals by physicochemical means, such as variation of temperature, in order

to harry the existence of the bacilli and force them to produce some of their poisons."

The three types of "partial sera" prepared from these toxins are, (1) antitoxins "obtained by means of" ectotoxins, (2) antiendotoxins "obtained by means of poisons derived indirectly from the bacillary bodies," and (3) antibacterial sera produced by the inoculation into a horse of dead and, later, living microbes, after a preliminary prolonged and intensive vaccination. The proportions of these sera are varied according to the individual case. Thus, for pulmonary tuberculosis there must be a predominance of antitoxins, while for surgical tuberculosis antiendotoxins must predominate. In pulmonary tuberculosis antitoxins and antibacterial sera against the common secondary invaders are administered. In abdominal tuberculosis sera are also given by mouth. Injections are made directly into infected glands.

The aim of this antitoxic treatment is to destroy the poisons generated within the body, thereby enabling the body to more successfully elaborate its own defenses. In this way, the rapid development of the disease is stopped, and the condition is changed from an acute to a chronic one. It is not claimed that treatment by passive immunization is curative. "Although a clinical recovery is brought about by the serum, relapse or a re-infection is always possible because the passive immunization has not modified the natural resistance of the patient to tuberculous infection."

Active immunization is employed in the chronic forms of tuberculosis. "Various antigenic elements of the bacillary protoplasm are injected separately into the patient in order to secure a series of immunities against all the deleterious products of bacterial disintegration." The author emphasizes the importance of maintaining the strength and specificity of these partial antigens during their preparations. He states that in the preparation of the vaccine the ectotoxins must be removed from the bacillary bodies. He utilizes a mixture of antigens and antibodies in the belief that active immunization is thereby facilitated and that undesired reactions are avoided.

Various vaccine combinations are employed, but the final dosage must contain all the antigens. The treatment extends over a period of a few months.

The illustrative cases reported are eight in number and are characterized by some vagueness in description. This may be because the article is in the nature of a general summary. Nevertheless it is regrettable. Three roentgen plates are shown but they are on three different patients, so that no comparison can be made. The most striking improvement is found in case 4 which is reported as follows.

"October, 1916: Pulmonary tuberculosis diagnosed, went into the country. 1918: To Sabourins sanatorium, T. B. in sputum, temp. 100.4°-100.8° F. Returned to Paris not cured. Lost 11 lbs. in one month. To Riviera, gradually getting worse. April, 1919: In bed with temperature 102.4°; Haemoptysis lasting for three weeks. Up for a short period, then returned to bed where she remained until April, 1920, when condition was very critical. Violent and continuous cough, paroxysms lasting for as long as 20 minutes, expectoration green and purulent (350 c.c. per day). Drenching sweats, extreme emaciation, com-

plete anorexia. Pulse rate 140, temperature 105.8°, insufferable headaches, delirium; death imminent. April, 1920: intensive Spahlinger treatment. Four injections of partial antitoxin No. 2 were given per day (morning, noon, afternoon and evening) and 10 c.c. of serum by mouth 12-hourly. In 15 days the cough had practically ceased. Temp. fell from 105.8° to 99.5°, and the pulse-rate from 140 to 78. Amount of expectoration dropped from 350 c.c. to three or four daily expectorations. Appetite quickly restored. Night sweats diminished in frequency, but did not entirely cease until expiration of two months. Although after a fortnight nearly all signs of intoxication had gone, the intensive treatment was continued for a further period of one month and then gradually reduced to two injections of serum weekly. In August the patient came to Geneva. She gained 1st 10 lbs. in four months. X-rays showed total opacity of the whole of the left lung and the right base. September, 1920: Examination showed no pulmonary activity. April, 1921: Re-examined, no active physical signs, patient cured."

—*W. T. V.*

The Etiology of Rickets

POSSIBLY our readers may be inclined to the opinion that there is at present in current medical literature an excess of articles on this subject, but, after reading a very interesting review by Findlay* we cannot resist the temptation to briefly run over the theories concerning this disease. These may be grouped as follows:

(1) *The Calcium Deficiency Theory.*—In the first study of rickets it was quite evident that the most characteristic and striking pathologic condition is the deficiency of calcium in the bones. This might result from any one of the following conditions: (a) a deficient supply of calcium in the food; (b) imperfect absorption of calcium from the intestinal canal; (c) inability on the part of the growing bones to fix calcium in their substance, and (d) inability on the part of the bones to retain the calcium assimilated. Following this theory, rickets was believed by many to be due to deficiency of calcium in drinking water. Many investigators attempted to induce this disease in animals by reducing the amount of calcium in the food. Since calcium is an essential constituent of the bones, if there be none or an inadequate amount in the food, the bones cannot grow normally. This follows as an incontrovertible fact. The same thing is true of phosphorus. Some of the early experimenters, notably Roloff and Voit, on calcium deficient diets induced in animals changes which they believed to be those characteristic of true rickets, but when the etiology of the disease was better understood the results following deficient calcium diets were shown to be merely an osteoporosis. Moreover, experimentation soon demonstrated that rickets does occur sometimes in animals in which there is no calcium deficiency in the food and no imperfection in absorption can be demonstrated. It is evident that there is still much work to be done under the

*The Lancet, 1922, i, 825.

calcium deficiency theory. Most of the experiments on this theory have been carried on for too short a time to justify final conclusion. It is easy to demonstrate, as has been done repeatedly, that rickets may develop when the food contains even an excess of calcium, but this throws no light upon the question of either the assimilation of the calcium by the bone or the bone's ability to retain the calcium which has been absorbed. Wells has shown by introducing cartilage into the peritoneal cavity of a rabbit that the calcium is absorbed in proportion as it is destined to become calcified. Findlay and his colleagues have repeated this experiment and have found that rachitic cartilage absorbs more calcium than does normal cartilage. Kramer and Howland find no alteration in the calcium content in the blood in rickets, but have been able to detect a very definite deficiency of inorganic phosphorus.

(2) *The Infection Theory.*—Many years ago the claim was made, notably by certain French and Italian observers, that rickets is an infectious disease, and in 1911 Robert Koch stated that he could induce rickets experimentally in animals by the injection of streptococci. More exact study of this matter has shown that the changes induced by a chronic poisoning with a streptococcus protein have not the slightest resemblance to rickets. Findlay and colleagues at the University of Glasgow have attempted to obtain evidence of a specific antibody in rickets by means of the complement deviation test. They employed as antigen, watery and alcoholic extracts of rachitic cartilage from the ends of long bones and ribs. These experiments were entirely negative and, consequently, lend no support to the infection theory. The same investigators tested the infectious nature of the disease by injecting puppies with blood recently drawn from rachitic children. These treatments had no effect upon the health or growth of the animals; indeed, it is stated that finer puppies were never seen in the laboratory. Some one has suggested the idea that rickets might be due to a virus transmitted by body lice. However, this suggestion may be dismissed, because it is well known that children who have always been free from body lice may have and do have rickets. Findlay calls attention to the fact that he found flea bites more freely in rachitic than in nonrachitic children. In his own studies he observed that without exception rachitic children were flea bitten, often badly, but that nonrachitic children were not bitten at all. This, however, he is inclined to attribute to the poor parental care and bad hygienic conditions under which his rachitic children lived, and he does not believe that the flea bite is a factor in the etiology of the disease.

(3) *Deficiency of Fat in the Diet Theory.*—Along in the eighties Bland-Sutton stated that rickets would appear in young animals if they were wholly deprived of milk, whatever the diet might otherwise be, but, almost immediately following this announcement, Baxter showed that Bland-Sutton's animals had not developed rickets, but marasmus. Furthermore, the same investigator saw rickets develop in his control animals fed upon milk and oatmeal. The last mentioned investigator had among his controls one puppy which he intended to give to a friend and on account of his special interest in this animal, he frequently gave it exercise, while the others were kept in their kennels. He observed that all appearances of rickets in this animal vanished after a long

period of exercise. This set Baxter to thinking and he took a litter of puppies, divided them into two lots, both were fed upon the same diet, consisting of milk, porridge, and horse flesh, all were housed in the same room, some were confined in a cage while others were allowed freedom and on occasions were taken out for walks. The confined animals became markedly rachitic, while those allowed their freedom did not.

(4) *The Vitamin Theory.*—Mellanby, at the University of Cambridge, has for the past few years been engaged in a series of experiments on the etiology of rickets. He has convinced himself that this disease is due to a diet deficient in a vitamin in some way connected with the fat of the food. He does not think that the disease is due to the absence of fat as fat, but because there is linked to the fat an antirachitic vitamin identical with or similarly connected with the fat, as is the case with fat-soluble A. Paton, of the Glasgow School, has contested this claim. Of two litters of pups in a metabolic study, five were sent to the country, being fed on a diet of porridge and skimmed milk. The daily intake of fat was not more than 2.8 grams. These animals had abundant exercise. The controls, kept at home in the laboratory, fed on porridge and whole milk, with an occasional addition of butter, so that the daily intake of fat, at first three grams, rose to six, and in some instances this increase in fat was carried to 14.5 grams. All the puppies kept in confinement, on being killed when eleven weeks old, showed signs of rickets, those receiving the greatest amount of fat being most severely affected, while those on a scant fat diet but exercised in the country, remained pefectly normal. It seems that Paton and his helpers have demonstrated that Mellanby's claims are unjustified.

(5) *Insufficient Exercise Theory.*—Findlay thinks he has evidence, both from experimental and from clinical sources, that the most potent factor in the causation of rickets is lack of exercise. We have already, under the preceding heading, given an illustration of the experimental evidence. Findlay and his assistants have studied the effects of environment, especially of housing, on rickets in Glasgow. They found that the average air space per person in families where marked active rickets was present was 396 cubic feet; in cases of slight rickets, 452 cubic feet, and in families where there were no rachitic children it was 565 cubic feet or more. Rachitic families were twenty per cent larger than nonrachitic and in the former the health of the mother was bad in nearly thirty per cent, while in the latter this was true in only five per cent. Diet did not seem to play any important rôle in the development of rickets. The average caloric intake per man in the rachitic families was 3315 and in the nonrachitic families, 3390. In the rachitic families twenty per cent consumed less than 3000 calories per day, while this held good for twenty-five per cent in the case of the nonrachitic. Recently Hutchison has studied the relation between housing and dietetic conditions and the prevalence of rickets among the rich and the poor in Nasik in India. It is the custom of wealthy Hindoos and Mohammedans in that region to confine their children in airless and sunless rooms, not only during infancy, but also in the case of girls until puberty or until marriage. On the other hand, the poor live in huts or tents and practically lead an outdoor life. The articles entering into the diets of the two classes

are the same in quality, but of course, different in quantity. There is practically no difference between the energy value of the diets of the two classes, but in the poor much less of this is represented by fat than in the case of the rich; and what is more important, in the diet of the rich the fat is present chiefly in the form of milk, whereas in the poor, animal fat is often absent from the diet altogether and if present, only in small amounts. Hutchison found early rickets during infancy and late rickets at more advanced ages prevalent among the rich and scarce among the poor. Moreover, he found that when the rachitic children of the rich were placed in the sun and fresh air, no change in diet being made, they recovered rapidly.

(6) *The Sunshine Theory.*—It is an interesting fact that Glisson, the first to observe this disease, called attention to its prevalence in dark, foggy places hidden away from the sun, and it grows more evident from all the experiments that are being made that sunshine is an important factor in the prevention of this disease. Of course, the adjuvants, proper diet and adequate exercise must not be forgotten.

—*V. C. V.*

OBITUARY

G. SIMS WOODHEAD

THOSE of us in America who have had the pleasure and honor of entertaining Dr. Woodhead in our homes have learned with deep regret of his untimely death in December, 1921. He was the son of a Yorkshire newspaper man and was born in 1855. He began his medical studies at the University of Edinburgh in 1873 and graduated in 1877. Soon thereafter he was appointed an assistant to the professor of pathology, in which position he soon attained distinction, both as an investigator and as a teacher. In 1883 the first edition of his splendid work on Practical Pathology was issued. Woodhead's success as a teacher and organizer in Edinburgh led to his being called to be the first superintendent of the Laboratory of the Royal College of Physicians in London. Here continued success was secured and in 1899 he was called to fill the very important chair of pathology at the University of Cambridge. In 1901 he became a member of the Royal Commission on Tuberculosis, and to his work on this Commission we are largely indebted for the facts which we now have establishing the responsibility of the bovine tubercle bacillus in the causation of human tuberculosis. It will be remembered that in 1901 Koch stated that in the warfare against tuberculosis the milk problem might be altogether neglected, since the bovine bacillus plays no part, or at least an unimportant part, in the causation of tuberculosis in human beings. Woodhead, in England, with his confreres, and Park, in this country, demonstrated beyond question that, in children at least, the bovine bacillus is an important factor in the causation of

tuberculosis and that we can by no means ignore the possibility, indeed the certainty, of the distribution of this disease through infected milk.

From early manhood Dr. Woodhead was an enthusiastic supporter of the Volunteer Medical Corps, and at the outbreak of the European War he was placed in medical charge of the Irish Command Depot in Tipperary. During the later years of the War he acted as consultant and as inspector of laboratories throughout the Kingdom. At the close of the War the tuberculous soldier received his special attention and he did not spare himself in the organization of sanatoria and colonies for the benefit of these men. He founded the Journal of Pathology and Bacteriology, was one of the leading supporters of the Pathological Society of Great Britain and Ireland, and was a member of the Executive Committee of the Imperial Cancer Research Fund. He also served on the Treasury Committee of the Scottish Universities, and his advice was generally sought throughout the British Empire. He was a total abstainer, and will be remembered not only for the scientific and practical work that he did, but for the cheer and good comradeship which he carried with him wherever he went. —*V. C. V.*